FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

Biological Responses to Metal Implants

September 2019

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1 INTRODUCTION

For more than 100 years, metals and metal alloys (a combination of metal elements) have been commonly used for a host of medical implant applications across most medical specialties. The clear majority are regulated by the Food and Drug Administration (FDA) as Class II (moderate risk) devices and cleared for marketing through the premarket notification ["510(k)"] pathway after demonstration of "substantial equivalence" to a legally-marketed Class II device or granted a De Novo request, or as Class III (higher risk) devices approved through the Premarket Approval Application (or PMA) process after demonstration of a reasonable assurance of safety and effectiveness. As part of their premarket evaluation, these products undergo a battery of nonclinical (bench and/or animal) tests – often following specific FDA guidance documents or national/international standards. These results, along with clinical data in certain circumstances, are provided to, and reviewed by FDA prior to market authorization.

In the past several years, FDA has undertaken extensive postmarket reviews of data associated with specific metal-containing implants after safety concerns were raised including for metal-on-metal (MoM) total hip arthroplasty (THA) systems and the Essure System for permanent birth control.[1] In those cases, the potential role of metal components in the development of local and systemic adverse events had been questioned. In the former example, metal wear/debris was determined to be associated with the occurrence of local pseudotumors and aseptic loosening of the prosthesis with subsequent need for revision. Some have also raised concerns over the association of elevated metal ion levels with neurological events. For the latter (Essure System), the patient-reported associations with broad systemic signs/symptoms (considered by some to represent "allergic" or "hypersensitivity" reactions) are less clear. Together, these issues have raised questions about how an implant or insert recipient's immune system may respond to the presence of metal in/from the device and to what degree, if any, that response may produce clinically significant signs, symptoms or adverse outcomes.

[1] For additional history on these systems please visit: https://www.fda.gov/medical-devices/implants-and-prosthetics/metal-metal-hip-implants and https://www.fda.gov/medical-devices/implants-and-prosthetics/essure-permanent-birth-control

This paper presents FDA's review of currently available scientific information related to metals and their uses in medical implants, with focus on how metal materials are impacted by a physiological environment, expected and potential immune system responses to the metal associated with an implant, as well as subsequent clinical manifestations. It is the result of a collaborative effort amongst subject matter experts (SMEs) gathered from across the Center for Devices and Radiological Health (CDRH), the organization within the FDA that is charged with regulating medical devices. Just as importantly, this paper identifies where gaps exist in the scientific evidence related to immunological responses to metal-containing implants, and where opportunities for further research exist and will serve as a starting point for a public discussion on November 13 and 14, 2019 as part of an advisory panel meeting.[2]

The paper focuses on those metals and alloys which are commonly used in the medical device industry for implants.[3, 4] A list of acronyms commonly used in this paper has been provided in Appendix A.

[2] For more information on the panel, the reference to the corresponding regulatory document will be updated/added once a publicly available federal register notice has posted.
[3] Dental amalgams will only be mentioned briefly as a separate review has been conducted and will be presented.
[4] Ceramics such as titanium oxide and elastomers such as silicone-based materials are not included as part of this paper.

2 BACKGROUND: DEFINITIONS, HISTORY, AND LANDSCAPE

Implants are routinely used to address many different conditions in almost every medical specialty. Many of these devices allow physicians and patients significant, effective advantages over alternative surgical and medical options, and may provide a treatment when no other option exists. These advantages have led to continued interest in the development of implanted devices over the last century.

The term "implant" refers to a wide variety of different medical devices, from solid metal implants, such as orthopedic plates/screws, to bioelectronics such as pacemakers or neurostimulators. Some implants are temporary and may be designed to be removed or replaced, while others are meant to be permanent (i.e., not intended to be removed). For this paper, implants are defined as medical devices that are placed into a surgically or naturally-formed cavity of the human body and are intended to remain there after the procedure for an extended period. This review primarily focuses on implants with metal parts or components that have contact with body tissue.

Implant components based on metallic elements are chosen as a biomedical material because they have numerous advantages over other materials, including high mechanical strength, durability, good thermal and electrical conductivity, ductility, and chemical/biological compatibility. However, the types and uses of early devices were limited due to a lack of available materials. It has only been in the last 100 years that implantable medical devices have become commonplace in healthcare.

The first attempts at using metal implants outside of dental implants occurred in the late 19th century with the development of the "Lane Plate," which was an internal fixation plate used to treat bone fractures (Lane 1895; King 1959; Uhthoff, Poitras, and Backman 2006). The development of aseptic operating room techniques used to limit patient exposure to bacteria was a turning point in allowing for the implantation of these devices (King 1959). However, these first devices, made from various alloys available at the time, were susceptible to problems with corrosion (King 1959; Uhthoff, Poitras, and Backman 2006).

The development of stainless steel and vitallium (cobalt-chromium-molybdenum alloy) in the early 1900s was a landmark development and starting point for modern metal implant development (King

1959; Disegi and Eschbach 2000; Gore et al. 2005; Abraham 2014). From there, the development of metal implantable devices continued to expand into orthopedic, dental, and cardiac areas in the mid-20th century (Greatbatch and Holmes 1991; Uhthoff, Poitras, and Backman 2006; Knight, Aujla, and Biswas 2011; Joung 2013; Abraham 2014; Saini et al. 2015).

The first generation of hip implants was introduced in the 1950s and 1960s and included metal-on-metal designs with cobalt-chromium alloys (Knight, Aujla, and Biswas 2011). At the same time, the development of miniaturized circuitry allowed for the development of pacemakers, with the first pacemaker being implanted in 1958 (Joung 2013). In subsequent years, advances in technology allowed for metal implants to branch into nearly all medical specialties for the treatment and management of numerous different diseases and conditions. Some developments of note include the first implantable neurostimulator in 1967 (Mullett 1987; Mekhail et al. 2010) and the first balloon-mounted arterial stent in 1985 (Palmaz et al. 1985; Serruys , Kutryk , and Ong 2006).

The most common metals used in implants have historically been stainless steel (iron-based alloys), cobalt-based alloys (Co-based), pure titanium, and titanium-based alloys (Ti-6Al-4V). Various refractory metals (metals which are difficult to fuse or corrode), such as molybdenum (Mo), tungsten (W) and tantalum (Ta), have also been used as alloying elements in implantation materials. Noble metals, such as gold (Au), silver (Ag), platinum (Pt), and iridium (Ir), are common in implants with electronic components (Khan et al. 2014). The use of a particular metal or alloy depends on the application; for example, surgical grade stainless steel is known for its high strength and good ductility, but can be difficult to integrate with bone or soft tissue (Khan et al. 2014). As a result, stainless steel is commonly used in fracture fixation devices and/or temporary implants intended to be removed at a later time. On the other hand, Co-based alloys (e.g., Co-Cr-Mo, Co-Cr-W-Ni) are highly corrosion resistant, have higher strength and hardness, but have lower ductility and are harder to work and configure by machine (Khan et al. 2014; Matusiewicz 2014). Therefore, Co-based alloys are used more widely in longer-term permanent implants and those that require high wear resistance, such as artificial joints or hip prostheses (Khan et al. 2014).

The alloy known as nitinol (Ni-Ti) is being used more frequently in implants due to its shape memory behavior (i.e., ability to return to its original shape after a temperature change) (Elahinia et al. 2012), its superelasticity (i.e., ability to return to its original shape after removal of mechanical stress), and its biocompatibility when properly passivated. Ni-Ti is now used extensively in vascular stents and is being used in implants in various other applications such as orthopedic fixation devices where its unique properties may be advantageous.

Recent developments in materials chemistry, metallurgy, and manufacturing continue to spur innovations in design and diversification in materials utilized in metal implants. For example, additive manufacturing (e.g., 3D printing), is increasingly being utilized to produce custom shapes and geometries using a variety of metals, adding to the potential applications of metal implants.

Because of continued technological development and engineering advances, the number and types of metal implants available on the market has increased in recent years. As can be seen in the Table of Appendix B, the current spectrum of metal implants available today is diverse.

3 METALS IN HUMAN PHYSIOLOGY AND PATHOLOGY

Some metals which are commonly found in implants, such as copper, zinc, iron, manganese, and cobalt are examples of elements that are essential to our normal biological functions. These metals are required only in small amounts and are critical to the structure and/or function of many proteins and enzymes. Abnormal function may occur, along with associated signs or symptoms, when there is too little (deficiency) of an essential metal. Other metals used in metallic implants such as nickel, titanium and aluminum are nonessential for human health. Both essential and nonessential metals when present at sufficiently high concentrations can disturb normal biological functions and result in cellular stress responses known as metal toxicity. Metal toxicity may affect various tissues including the kidney, liver, heart, the immune and nervous systems.

3.1 INTRODUCTION

As noted in Section 2, numerous different metals, either alone or as part of an alloy, are included in the design of medical implants. This section will summarize the physiological role of elemental metals which are more commonly incorporated into devices. For those metals which are required for normal human function (e.g., "essential elements"), information will be presented about the signs and symptoms of elemental deficiency and excess (*e.g.*, toxicity). For non-essential metals, discussion will focus largely on toxicity.

It should be noted that the toxicity information is typically based on exposure to the element through dietary intake and/or occupational/environmental exposure (e.g., dermal contact, inhalation). However, since the *in vivo* implant environment and the form/composition the metal appears in that environment (*e.g.*, chemical form (valence), physical form (particulate vs ionic), dose released over time, etc.), may be

different or unknown (Brown et al. 2015), the degree to which published toxicity data can be extrapolated to a patient implanted with a metal-containing device is not known.

3.2 Essential Trace Metal Elements

Trace elements are those which are present in only small amounts within a given environment. When such an element is critical to the structure and/or function of a living organism, it is considered an essential trace element. An element is generally considered to be essential if it is present in living tissues at a relatively constant concentration; evokes similar structural or physiological anomalies when removed from the organism; and those anomalies are prevented or resolved by supplementation of the element.

Essential metals, in appropriate amounts, are critical to the function of numerous human proteins and enzymes (metalloproteins and metalloenzymes, respectively) and it is estimated that greater than 30% of human enzymes require at least one essential trace metal for proper function (Waldron et al. 2009). Because they are only required in small amounts, they are under tight homeostatic regulation in terms of absorption, transport, distribution, storage, recycling, and excretion from the body.

Table 1 below summarizes information related to the key essential metals which may be seen in different medical implants. It also includes two metals whose status as an essential element have been debated (chromium and vanadium).

Table 1 Essential Metal Elements

Metal	*Major Physiological Roles of Proteins Utilizing the Metal*	*Key Manifestations of Deficiency*	*Potential Toxicities or Manifestations of Excess*
Cobalt (Co)	Metabolism of purines/pyrimidines amino acids, fatty acids, folate	Anemia Neuropathy Neurocognition changes	ACD* Cardiomyopathy Polycythemia Altered thyroid function
Copper (Cu)	Collagen cross-linking Bone formation Iron metabolism Hemostasis/thrombosis Neurotransmitter synthesis Free radical control	Iron-refractory anemia Neutropenia/infection Osteoporosis Neurological dysfunction	GI symptoms Hemolysis Cardiac failure Renal failure Hepatic dysfunction Alzheimer's
Iron (Fe)	Oxygen transport Oxygen storage DNA synthesis/repair RNA transcription Synthesis of collagen, neurotransmitters Energy metabolism Immune function	Microcytic anemia Diminished thyroid function Impaired neutrophil function Impaired cognition	Free radical generation GI symptoms (acute) Hemochromatosis • Cardiomyopathy • Cirrhosis • Diabetes • Arthritis
Manganese (Mn)	Metabolism of carbohydrates, lipids Neurotransmitter synthesis Bone/cartilage formation Urea metabolism Control of free radicals	Dermatitis Weight loss Growth retardation Abnormal bone/cartilage Dyslipidemia Glucose intolerance	Headache Psychiatric symptoms GI symptoms Parkinson's-like signs/symptoms
Molybdenum (Mo)	Metabolism of amino acids Metabolism of purine/nucleotides, UA Metabolism of drugs/prodrugs Metabolism of neurotransmitters	Urinary tract stones Acute renal failure, Myositis Mental changes/coma	Elevated uric acid/gout Secondary copper deficiency Reduced testosterone
Zinc	Protein and carbohydrate metabolism	Skin/mucosa changes	GI symptoms (acute)

(Zn)	Immune function Wound healing DNA synthesis and repair Control of free radicals Stabilization of protein structure Intracellular signaling	Decreased immune function Delayed wound healing Neurological dysfunction Bleeding abnormalities Osteoporosis Delayed growth	Copper deficiency Myeloneuropathy.
Chromium (Cr)	Glucose metabolism/tolerance Lipid metabolism	Impaired glucose tolerance Abnormal lipids profiles Peripheral neuropathy	Cr3+ • Potential liver issues • Potential kidney issues CR6+ • Respiratory symptoms • Dermatitis/ulcerations • GI symptoms • Lung cancer
Vanadium (V)	Phosphate metabolism Insulin enhancement Lipid metabolism		GI symptoms Headache Weakness Tremor

*Abbreviations: ACD: Allergic contact dermatitis; GI: Gastrointestinal; UA: uric acid

3.3 NON-ESSENTIAL METALS

Although not considered essential to human health, other metal elements may impact human physiological processes as described in Table 2 below.

Table 2 Non-Essential Metals Found in Implants

Metal	Potential Adverse Effects	Other Commercial Uses
Nickel (Ni)	Delayed hypersensitivity Acute: GI symptoms, headache, vertigo, vision changes Chronic: • Altered iron metabolism • Cardiovascular, respiratory or kidney disease • Alteration in hemostasis of calcium, magnesium, manganese, zinc	
Titanium (Ti)	Suppression of osteogenic differentiation Yellow nail syndrome	Has been used in sunscreens, anti-tumor preparations
Aluminum (Al)	Osteomalacia Hepatic dysfunction Anemia Dialysis encephalopathy (dementia, myoclonus) Association with Alzheimer's	Frequently used in antacids, toothpaste, antiperspirants, sunscreens
Silver (Ag)	Local argyria (blue-grey skin or organ discoloration)	Sometimes used for anti-microbial properties
Gold (Au)	Bone marrow suppression Dermatitis Glomerulonephritis Vasculitis Hepatotoxicity Neuropathy	Intramuscular gold therapy has been used in conditions such as rheumatoid arthritis
Palladium (Pd)	Lip edema Itching Respiratory symptoms	

Platinum (Pt)	Certain Pt-containing compounds may cause respiratory symptoms including kidney toxicity, hearing loss, bone marrow damage	Cisplatin in Cancer therapy
Tin (Sn)	Acute: GI symptoms, headache Altered metabolism of zinc, iron, copper Cholesterol metabolism	
Tungsten (W)	Certain compounds may antagonize molybdenum	
Iridium (Ir)	Some salts may cause allergic reactions (ACD)	

*Abbreviations: ACD: Allergic contact dermatitis; GI: Gastrointestinal; UA: uric acid

4 CURRENT NONCLINICAL PRE-MARKET EVALUATION OF METAL IMPLANTS

Various nonclinical and clinical assessments can be used to understand whether materials used to manufacture medical devices can cause adverse biological responses. Corrosion and other physical or chemical processes can lead to the release of metal ions and small particles, which may cause adverse tissue responses at the site of the implant, as well as in other places in the body. For metal devices, immunological reactions and local changes in tissues surrounding an implant are the most commonly reported issues. To help understand how the host body responds to metal devices, the FDA uses a combination of nonclinical studies on corrosion, the release of metal ions (see "Corrosion and metal ion release"), device-specific fatigue testing as well as animal and clinical studies (see "Clinical response to metal implants") on biological responses. The FDA uses this information to evaluate biocompatibility issues, such as risk of immunological response, tissue destruction or overgrowth, and other adverse reactions.

4.1 INTRODUCTION

Manufacturers who wish to introduce a metal-containing implant to the U.S. marketplace for a medical purpose must submit a marketing application to the FDA for review and marketing authorization prior to introducing the device to the market, unless the device is exempt from 510(k) and GMP requirements per https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/315.cfm. Nonclinical testing (e.g., bench testing and in some cases, animal testing) conducted by the manufacturer to characterize their device and its materials is reviewed by a multi-disciplinary team at FDA as part of its decision-making process. This section provides an overview of the typical testing which is recommended and evaluated by FDA as part of its review of a metal-containing device. Many of these tests are further explained in FDA-issued Guidance Documents or FDA-recognized national or international standards which can be found at the FDA website and are listed in Appendix C. For many of these assessments, medical device manufacturers

often compare the proposed new or modified device to a predicate or reference device to demonstrate acceptable performance in a particular area.

4.2 BIOCOMPATIBILITY

For sterile and non-sterile devices that come into direct or indirect contact with the human body, CDRH's 2016 Biocompatibility Guidance (FDA 2016) describes what type of information is helpful to evaluate the potential for an unacceptable adverse biological response resulting from contact of the component materials of the device with the body.

When selecting the appropriate endpoints for biological evaluation of a device, FDA considers the chemical characteristics of the device materials and the nature, degree, frequency, and duration of exposure to the body (i.e., intended use), as outlined in Attachment A of CDRH's 2016 Biocompatibility Guidance. ISO 10993-1 "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process" categorizes contact duration into three categories: limited (i.e., ≤24 hours), prolonged (i.e., >24 hours to 30 days), or permanent/long term (i.e., > 30 days).[5] These same definitions are used by FDA when considering biocompatibility endpoint assessments.

Biocompatibility endpoints described in the 2016 CDRH Biocompatibility Guidance which could be impacted by metallic components in, on, or from a metallic device include: cytotoxicity, sensitization, irritation or intracutaneous reactivity, acute, subchronic and chronic systemic toxicity, material-mediated pyrogenicity, genotoxicity, implantation, hemocompatibility (hemolysis, complement activation, thrombosis), carcinogenicity, reproductive or developmental toxicity, and biodegradation (for absorbable materials). As described in the 2016 CDRH Biocompatibility guidance, for biocompatibility tests requiring extraction of the device, single or multiple extracts may be needed to assess both polar and non-polar chemicals that can be released from the device. Additional information is provided below on how several of these endpoints are considered by FDA in the biological evaluation of implanted metal devices.

4.2.1 Sensitization

Exposure to metal ions can lead to both local and systemic hypersensitivity reactions. Metal hypersensitivity is generally believed to be a Type IV (delayed hypersensitivity) reaction mediated by T lymphocytes (also called "T cells", these are a subtype of white blood cells which are involved in cell-mediated immunity). In reactions attributed to Type IV hypersensitivity as the primary mechanism, the metal ions released from implants are believed to act as haptens. Haptens are chemical moieties which are too small to elicit this type of immunogenic response by themselves but are capable of binding to endogenous (internal) proteins to form hapten-protein complexes which act as antigens (Svedman et al. 2014); (Traidl et al. 2000). The hapten-protein complexes are then processed by the antigen-presenting cells and presented to T cells that are the key mediators of delayed type hypersensitivity reactions (see "Subclinical response to metal implants" for additional details). Clinical manifestations potentially relevant to systemic hypersensitivity reactions are discussed in more detail in "Clinical response to metal implants."

[5] ISO 10993-1:2018 changed the category from "permanent" to "long-term" for all devices used for > 30d to account for devices that are absorbed or removed.

The sensitization or allergenic risk is typically evaluated for all metal implants regardless of contact duration and the nature of tissue contact. ISO 10993-10 provides guidance on skin sensitization testing for devices but does not include any methods specific to systemic sensitization. Currently, there are three animal assays used to assess skin sensitization [delayed type (Type IV) hypersensitivity] potential of chemicals from devices including metal implants (NIH 2010):

- Guinea Pig Maximization Sensitization Test (GPMT),
- Guinea Pig Closed Patch Sensitization Test (Buehler Test), and
- Mouse Local Lymph Node Assay (LLNA).

Methods for these three tests are described in ISO 10993-10:2010 (ISO 2010). See Appendix C for status of CDRH's recognition of this and other biocompatibility standards. The GPMT is considered the most sensitive of these tests due to the use of Freund's Complete Adjuvant (FCA) to stimulate the immune system and is the most common method used for assessments of devices including those made with metal. The Buehler test is typically used for devices with intact, or unbroken, skin contact, including those made from metal and other materials.

The LLNA can be used for testing metal compounds, except for nickel and nickel-containing metals, unless there are unique physicochemical properties associated with these materials (*e.g.*, nanomaterials) that may interfere with the ability of the LLNA to detect sensitizing materials. FDA reviews the LLNA data for devices on a case-by-case basis. Nickel ion skin sensitization in humans involves the direct activation of human Toll-like receptor 4 (TLR4) by nickel ions. However, this does not occur in the LLNA assay. Direct activation of TLR4 by nickel ion fails to generate skin sensitization response in mice in the LLNA assay because the structure of TLR4 in the healthy, wild type mice used in the LLNA assay is not the same as that of the human TLR 4 (Schmidt et al. 2010). However, there are other mechanisms proposed for nickel sensitization in mice which are independent of TLR4 (Vennegaard et al. 2014). In addition to or instead of an animal assay, clinical studies might also be used to assess sensitization potential.

While not included in ISO 10993-10, the human repeat insult patch test (HRIPT) can be used to assess skin sensitization in humans (*e.g.*, to support inclusion of labeling claims related to sensitization potential in humans) instead of the Buehler method. The American Standard of Testing and Materials (ASTM) published ASTM D6355 "Standard Test Method for Human Repeat Insult Patch Testing of Medical Gloves" (ASTM 2012), which provides information on how to assess sensitization potential of latex gloves in humans; a similar approach could be used for metallic devices in contact with intact skin.

There has been considerable debate regarding several diagnostic tests to evaluate patient sensitivity to metal including cutaneous patch testing, and *in vitro* assays such as the Lymphocyte Transformation Test (LTT). These tests have not historically been used for submissions to the FDA due to known limitations. Animal skin sensitization, human patch testing data, or LTT are generally not good at predicting the range of local and systemic immune responses including hypersensitivity to metal implants which are placed in non-dermal locations such as intravascular, orthopedic, gynecological, or dental implants. A fuller discussion of the limitations of these tests can be found in Section 8 below.

A better understanding of patient-specific mechanisms of immune responses to metallic implants would help to develop more predictive nonclinical and clinical tools for assessing the potential for skin and systemic hypersensitivity reactions to these implants.

4.2.2 Implantation

This section will focus on local response evaluations. For testing of systemic responses to devices please refer to Section 4.2.5.

The local toxicity of a device is generally evaluated by an animal implantation study as described in ISO 10993-6; "Biological evaluation of medical devices – Part 6: Tests for local effects after implantation" (ISO 2016). The final sterilized device, or a representative part of the device, is implanted into a clinically relevant tissue. Implantation studies generally include test devices and controls, an appropriate number of time points and are of sufficient duration to evaluate the local tissue response through the final device integration and/or absorption, and to evaluate a return to a steady state tissue response to the implanted device. Macroscopic and microscopic methods are used to evaluate the character and intensity of the local tissue response including parameters such as fibrosis, necrosis and inflammation.

A clinically relevant functional animal study is often used to evaluate the local tissue response in a relevant anatomical site under simulated clinical use conditions. Implantation studies can evaluate the local tissue response to metallic components in, on, or from a device. However, implantation studies designed specifically for biocompatibility assessments are not typically designed to evaluate the tissue response to mechanical failures, such as the generation of wear particles. It is well known that there are differences in the anatomy and mechanics between humans and animal models (Moran et al. 2016). These differences often prevent an adequate *in vivo* evaluation of the biological response to mechanical failure modes, such as coating delamination (separation into layers) or the generation of wear particulates. The biological risks resulting from mechanical failure are evaluated with additional studies that are designed to evaluate the *in vivo* response to device components that have failed mechanically (*e.g.*, for orthopedic implants, wear particles generated in a separate *in vitro* test system may be implanted into a relevant implant location).

4.2.3 Inflammatory Response

Inflammation is considered the body's normal response to tissue injury. The inflammatory response underlies most implant-related reactions, ranging from commonly expected wound healing processes to various exaggerated foreign body type and other (local and systemic) responses. As part of the body's normal host response, an implant may elicit a low-level *acute* inflammatory response which is generally of short duration, lasting minutes to days, depending on the extent of the implantation-related tissue injury. Myeloid cells such as neutrophils and macrophages are the primary cells involved in the expected acute inflammation with subsequent peri-implant wound healing. An implant may continue to elicit a *chronic* inflammatory response, lasting for months or longer and characterized by a broader immune cell infiltration including both myeloid and lymphoid cells. Chronic inflammation by implanted metal devices or metal wear debris may lead to adverse clinical effects. For example, sustained chronic inflammation at the implant-bone interface has been implicated for aseptic (free of infection) loosening of total joint replacements (Abu-Amer, Darwech, and Clohisy 2007; Gallo et al. 2013). As noted in Section 4.2.2, the local tissue response to a metal implant is currently evaluated in an implantation study by placing the implant at a clinically relevant site in accordance with the ISO 10993-6 standard or in a functional animal study conducted to evaluate the performance and safety of the implant. Histopathological evaluation includes characterization of inflammatory response by assessing the intensity of response as well as identifying the inflammatory cell types (*e.g.*, polymorphonuclear cells, lymphocytes, plasma cells, eosinophils, macrophages, multinucleated cells) involved in the tissue response.

While some aspects of inflammation are addressed in several of FDA's currently recognized standards, none of the currently existing standards provides all-inclusive guidance for comprehensive assessment of the overall inflammatory response that would incorporate nonclinical and clinical testing (see sections on "Subclinical response to metal implants" and "Clinical response to metal implants" for more details) because certain types of inflammatory responses to metals, and other select materials, in medical devices resulting in clinical manifestations (particularly systemic effects) had not been well-recognized in the past and are still the subject of debate, as described in this paper.

4.2.4 Genotoxicity and Carcinogenicity

Mutations and other types of DNA damage can be associated with cancer and heritable genetic diseases. The assessment of genotoxicity and carcinogenicity (cancer potential) are important components of the safety assessment of devices. The corrosion of metallic implants, generation of wear debris, or problems with the structural integrity of the metallic implants can lead to the release of metal ions which may potentially increase the genotoxicity and carcinogenic risk. Metals can cause genotoxicity and carcinogenicity by several different mechanisms. Induction of oxidative stress resulting in damage to cellular components including DNA, interference with DNA repair, and deregulation of cell proliferation are described as the three primary mechanisms associated with the genotoxic/carcinogenic effects of metals (Beyersmann and Hartwig 2008; Annangi et al. 2016).

FDA recommends that genotoxic and carcinogenic potential be assessed for all permanent/long-term (> 30 days exposure) metallic devices that fall in the following device categories:

1. Surface devices in contact with breached or compromised surface;
2. External communicating devices with direct/indirect blood contact or tissue/bone contact; and
3. Implant devices with tissue/bone or blood contact.

Also, the genotoxic risks are typically evaluated for metallic surface devices in permanent/long-term contact with the mucosal membrane and for the metallic external communicating and implant devices with prolonged (> 24 hours – 30 days) blood or tissue/bone contact.

Genotoxicity and carcinogenicity potential of a device can be evaluated by exhaustive extraction of the finished device and analysis of the extractables and leachables from the device in conjunction with a toxicological risk assessment of the identified and quantified extractables/leachables. Information on the risks from the device materials and processing can also be used in some instances to assess the genotoxic and carcinogenic risks. Genotoxicity testing is necessary if the genotoxicity profile of the device cannot be adequately established using a chemical characterization/toxicological risk assessment approach. Since no single test can detect all kinds of genetic damage, a battery of tests is recommended. For genotoxicity testing on the device, FDA recommends that the following two *in vitro* tests be conducted, as well as an optional third *in vivo* test:

1. Bacterial gene mutation assay: This test is conducted with engineered strains of *Salmonella typhimurium* and *Escherichia coli* designed to detect all possible single base pair changes as well as frameshift mutations [OECD 471 (1997) "Guidelines for Testing of Chemicals – Bacterial Reverse Mutation Test" (OECD 1997)].
2. An *in vitro* mammalian genotoxicity assay. A choice of one of the following is recommended:
    a. The Mouse lymphoma gene mutation assay [OECD 490 (2016) "Guidelines for the Testing of Chemicals – *In Vitro* Mammalian Cell Gene Mutation Tests Using the

Thymidine Kinase Gene"](OECD 2016c), is preferred since it detects the broadest set of genotoxic mechanisms associated with carcinogenic activity, including both gene mutations as well as chromosomal damage;

b. An *in vitro* chromosomal aberration (CA) assay [OECD 473 (2016) "Guidelines for the Testing of Chemicals – *In Vitro* Mammalian Chromosomal Aberration Test"] which detects only chromosomal damage (OECD 2016a); or

c. An *in vitro* micronucleus assay [OECD 487 (2016) "Guidelines for the Testing of Chemicals – *In Vitro* Mammalian Cell Micronucleus Test"] which detects only chromosomal damage (OECD 2016b).

3. FDA recommends that an *in vivo* cytogenetics assay be considered, for example, for devices containing novel materials. However, if the quantities of materials in the test extract following exhaustive extraction of the devices are below the threshold of detection of the *in vivo* assay, the test does not need to be performed.

The carcinogenicity assessment of a device depends not only on the genotoxicity information. There are some carcinogens that cause cancer via non-genotoxic mechanisms and carcinogenesis is also multifactorial. In addition to the genotoxicity data, other evidence such as human epidemiological data (if available), any relevant long-term clinical study data, or evidence of carcinogenicity from the long-term animal studies (*e.g.*, inflammation, pre-neoplastic lesions, or tumor findings in animal studies) may also be considered for assessing the carcinogenicity risks. Factors such as human relevance of animal data, available dose of any potential carcinogen (if present) from the device, location of the device implant site, as well as the propensity of the site to develop local tumors are some of the critical determinants in identification of the carcinogenicity risks from a device. Generally, a rationale is used to address carcinogenicity. However, if carcinogenicity testing is conducted, transgenic animal models such as the rasH2 transgenic mouse model may be used. For any carcinogenicity testing, FDA recommends that the sponsor discuss the carcinogenicity study design with FDA prior to initiating the study since none of the transgenic animal models have been formally validated for devices.

4.2.5 Systemic Toxicity

Systemic toxicity testing can be designed to evaluate both local and systemic responses to devices, but this section will focus only on systemic evaluations. See also Section 4.2.2 on implantation for local toxicity evaluations.

Systemic toxicity refers to adverse effects (other than systemic sensitization, genotoxicity, and carcinogenicity) that occur in tissues other than those at the site of local contact between the body and the device. The development of systemic toxic effects typically requires the release of chemical compounds from the device and distribution of these compounds to distant target tissue sites where deleterious effects are produced.

Systemic toxicity is included as a recommended endpoint in the biological evaluation of devices depending on the nature and duration of device contact with the patient (see Table A.1 of the CDRH's 2016 Biocompatibility Guidance (FDA 2016). The evaluation of acute systemic toxicity is recommended for essentially all devices except for devices that contact intact skin, regardless of the duration of contact, and those that contact mucosal membranes for less than 24 hours. FDA recommends that subacute/subchronic toxicity be evaluated for all devices with prolonged (> 24 hour-30 days) and permanent/long-term (> 30 day) contact with the patient, again except for devices that contact intact

skin. In addition, an evaluation of the potential for chronic toxicity to occur may be requested for devices with permanent/long-term tissue contact. A pyrogenic response (fever) to devices may be caused by material-mediated pyrogens including metal particulates and metal salts, as described in ISO 10993-11 "Biological response to medical devices – Part 11: Tests for systemic toxicity," Annex F (ISO 2006). Material-mediated pyrogenicity is generally evaluated using the rabbit pyrogen test (USP 2017).

There are three approaches that are typically used to assess the potential for adverse systemic effects to occur following the release of chemical compounds from a device:

1. Biological testing of extracts of the device in experimental animals;
2. Identification of the compounds extracted from the device using analytical chemistry methods and evaluation of the potential for systemic effects to occur using toxicological risk assessment principles; and
3. Leveraging of data from large animal studies or implantation studies where systemic information is included.

Each of these approaches for evaluating the potential for toxic systemic effects to occur has merits and limitations.

4.2.5.1 *Biological testing of extracts of the device in experimental animals*

Devices have traditionally been assessed for their potential to produce systemic toxicity using the biological testing approach that involves extracting the device in both polar and nonpolar solvents, then administering the extract of the device to experimental animals. Methods for conducting systemic toxicity testing are outlined in the ISO 10993-11 standard, "Biological evaluation of medical devices – Part 11: Tests for systemic toxicity" (ISO 2006). To minimize animal use, other data as described below can be leveraged to assess systemic toxicity.

4.2.5.2 *Chemical characterization/risk assessment*

As an alternative to the biological testing of device extracts, the chemical characterization/risk assessment approach, which does not require the use of animals, has gained increased acceptance to evaluate the potential for systemic toxicity to occur in response to compounds released from a device. In this approach, compounds are identified and quantified and the amount is compared to a health-protective threshold value, using the method described in ISO 10993-17 "Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances" (ISO 2002). Since threshold values are readily available for many of the metal ions and elements released from metallic devices, the implementation of the chemical characterization/risk assessment approach is typically feasible for most metals released from metallic devices.

A limitation of the chemical characterization/risk assessment approach is that it cannot typically be used to assess the potential for metal particles to produce adverse systemic effects unless toxicity data are available for particles with the same physical-chemical properties (*e.g.*, size, charge) as the particles released from the device and administered in the toxicity study by the clinically relevant route of exposure.

4.2.5.3 *Leveraging data from safety/efficacy studies in large animal or implantation studies*

Systemic toxicity endpoints can also be evaluated in safety/efficacy studies in large animal or in implantation studies of a device, if sufficient animals and appropriate controls are used. For evaluation

of systemic toxicity in these studies, the potential for adverse effects at distant target tissues is evaluated using clinical chemistry, hematology, and histopathology.

4.2.5.4 *General considerations for systemic toxicity assessments*

Humans and experimental animals respond similarly to the toxic effects of chemical compounds. Any systemic effects seen in routine systemic toxicity tests or in a large animal safety/efficacy study or in an implantation study are typically relevant for patients, unless there are mechanistic reasons to suggest that the results in experimental animals are not relevant for humans (*e.g.*, alpha-2µ globulin associated nephrotoxicity in male rats). This also applies when literature data is used to support the chemical characterization/risk assessment approach.

4.3 CDRH'S IMMUNOTOXICITY GUIDANCE

CDRH's Immunotoxicity Testing Guidance (FDA 1999) also provides information on how to evaluate potential adverse immunological effects of devices. It describes a systematic approach for assessing the immunotoxicological risks from devices. The first step of the assessment strategy is to determine if immunotoxicity testing is needed for the safety assessment of the device being evaluated or if scientific data exist to support the safety of the device in humans for its intended clinical use. If immunotoxicity testing is recommended, the guidance helps the user to identify what specific immunotoxicity tests could be performed. The guidance describes the five major immunological effects [hypersensitivity (Type I and Type IV), chronic inflammation, immunosuppression, immunostimulation, and autoimmunity] that might be associated with devices and provides examples of the specific types of tests that might be used for the evaluation of these immune responses. Humoral and T cell responses are commonly associated with the immunotoxic effects such as immunostimulation and autoimmunity and evaluated primarily utilizing the functional assays that determine the activities of the cells and/or organs (Clayton et al. 2014b; Hallab 2016); (Hallab et al. 2008). Routine testing for induction of autoimmune disease in animal models is not generally recommended.

5 CORROSION AND METAL ION RELEASE

Corrosion is the deterioration of a metal due to electrochemical reactions with its environment. Different corrosion mechanisms include: general or uniform (with or without an external source of electrical current), pitting (small holes on the metal surface), crevice (localized corrosion on a metal surface near or at the gap between two joining surfaces), fretting (caused by wear) and galvanic (different metals in direct contact). These corrosion mechanisms can result in the release of metal ions or other by-products. When released in sufficient quantities, these corrosion by-products may lead to adverse biological effects. Most device alloys form a protective oxide layer that reduces corrosion. Factors such as the biochemical and mechanical stresses associated with the implant environment can damage this protective layer and increase corrosion. Because the quality of the protective oxide layer can vary from one manufacturing technique to another, engineering testing is routinely done to evaluate the potential for corrosion of a specific device through different possible mechanisms. This testing is typically done under idealized conditions. While this enables comparisons between devices, it is still unclear how engineering (in vitro) performance correlates to the corrosion behavior when the device is inside the human body (in vivo). We typically see qualitative consistency between engineering testing and behavior inside the body. It is important to quantify these relationships using one or more of the following: computer models, engineering testing, tissue and body fluid evaluations (ex vivo), testing within the human body, (e.g., imaging and biopsies) and clinical studies.

5.1 INTRODUCTION

Understanding how metallic products change or degrade in different environments is an important concept when speaking about potential host responses. This section provides a summary of scientific information related to metal/metallic implant corrosion and test methods to assess those changes.

Corrosion is defined as metal degradation due to electrochemical reactions between the metal and its environment. For metallic implants placed in the body, these reactions (known as oxidation and reduction reactions) can cause release of metal ions at the implant surface resulting in degradation of the implant. The ramifications of corrosion are dependent on many factors (corrosion severity, type, etc.), and may lead to issues with device integrity or adverse biological responses. There are five common types of corrosion that may occur when a device is implanted: general, pitting, crevice, fretting, and galvanic corrosion (Gilbert 2017). Each of these is described in more detail below.

General corrosion/metal ion release is the uniform release of metal ions over an exposed surface. For metals with surface oxides, it has been shown that the amount of metal ions released from the implant is dependent on the composition and structure of its oxide layer (Sullivan et al. 2015). Typically, the release of metal ions is greatest immediately after implantation and the release rate reduces over time. However, in cases where the implant's oxide layer is not protective, release of metal ions may continue for longer durations and exhibit dramatic increases in release rate after implantation.

Pitting corrosion occurs when the surface of metallic devices develops localized pits or cavities that penetrate the surface of the device over time. Pits are initiated in specific regions such as inclusions, cracks, or other surface defects, which are sometimes unavoidable during manufacturing. This damage results in a release of metal ions (metal dissolution) into surrounding tissue. These "holes" in the device are typically round or cup-shaped, and if severe, may compromise the integrity or performance of the implant.

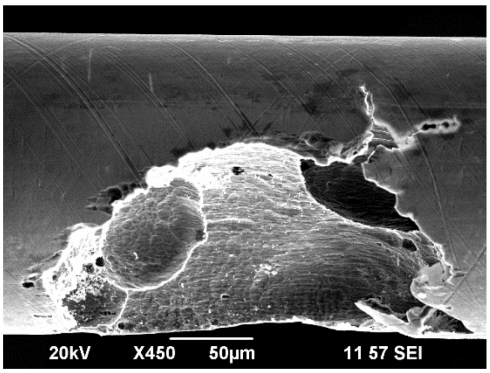

Figure 1: Example of pitting corrosion on the surface of stainless steel (Di Prima, Guiterrez, and Weaver 2017).[6]

Crevice corrosion occurs in localized areas where the metallic device is in contact with small volumes of stagnant (non-flowing) liquid. The chemistry of the local environment within these crevices can change, resulting in depletion (loss) of oxygen and a drop-in pH, making the metal surface more prone to corrosion. For example, modular orthopedic devices may facilitate local fluid stagnation increasing the potential for corrosion; even in metals that normally have good corrosion resistance.

Fretting corrosion occurs due to oscillatory (moving back and forth) micro-motion between contacting metallic surfaces. This motion can cause wear and disrupt the passive oxide film of the opposing metal surfaces. Even slight relative micro-motion between contacting surfaces may lead to continuous disruption of their passive films leading to corrosion of the exposed metal. The severity of fretting is

[6] *This work was performed by US Government employees and is in the public domain in the USA.*

dependent on many factors such as surface roughness, coefficient of friction of the metal surfaces, and mechanical properties. Fretting corrosion has been observed in devices that have modular designs such as hip and knee arthroplasty devices ((Higgs et al. 2013); (Arnholt et al. 2014)).

Galvanic corrosion occurs when chemically dissimilar metals are in contact inside the body. Corrosion is accelerated in one of the metals (anode or less noble), while the other metal (cathode or more noble) corrodes slower than it would alone. The rate of accelerated corrosion is determined by the voltage difference and surface area ratio between the different materials.

In this section, we provide an overview of the factors that influence the propensity for metallic implant materials to corrode and the *in vitro* test methods that are typically used to evaluate corrosion susceptibility. This is followed by a summary of reported observations of implant corrosion in vivo, along with a discussion of the challenges associated with predicting the behavior of these materials in vivo based on the results of *in vitro* testing.

5.2 Corrosion Susceptibility

Corrosion will only occur under conditions where a corrosion reaction is thermodynamically favorable, which in physiological environments is primarily dictated by the amount and type of dissolved ions and the electron affinity of the metal. Depending on these factors, a particular metal or metal alloy can be categorized as immune (to corrosion), passive, or corroding. Most medical device alloys, such as stainless steels, cobalt-chromium alloys, titanium alloys, and nitinol are passive under normal physiological conditions; they form a protective oxide surface layer in this environment that tends to inhibit corrosion. Other device components, such as marker bands and electrodes are comprised of metals such as platinum (Pt), iridium (Ir), tantalum (Ta), and gold (Au) and are highly stable and considered immune to corrosion under normal physiological conditions. Whether a device alloy is nominally considered corroding, passive, or immune under normal physiological conditions, there is a wide range of factors associated with medical devices and implant environments that can influence corrosion susceptibility. The most important of these factors, which include the (bio)chemistry of the local implant environment, mechanical interactions, applied electrical currents (active devices), and how the device alloys are processed during manufacturing, are detailed below.

5.2.1 Physiological Environment

The local physiochemical environment plays an important role on the corrosion performance of an implant. Local physiological factors such as pH, concentrations of ions and other small molecules, proteins, and cellular activity can influence the corrosion susceptibility of the metal (Pound 2019). Proteins at the implant site first adsorb onto the metal surface and aid in cell-metal interaction. Neutrophils and other cells of the immune system can secrete reactive oxygen species as a part of the foreign body reaction and cause a drop in local pH, which might increase corrosion susceptibility. Over time, as the implant integrates with the body, the local physiological environment will evolve as a part of the wound healing response. For example, in cardiovascular devices such as stents, the implant may cause local inflammation during placement, but gradual tissue coverage associated with normal inflammation in conjunction with blood flow will present a dynamic physiological environment to the stent. If corrosion is occurring, the local inflammatory response can be aggravated. For polymer-coated esophageal stents, low pH environment is the norm due to the presence of local gastric acid. Dental implants can experience a wide range of pH change because of a patient's diet. Hence, the corrosion susceptibility of a medical device is typically evaluated in a test solution that closely represents the physiological environment of the implanted device. When orthopedic and cardiovascular implants are tested for corrosion susceptibility, phosphate buffered saline (PBS) is often used because it achieves the

pH level and has similar inorganic components of blood and tissue. Other commonly used test solutions include 0.9% saline, Hank's buffered salt solution, simulated bile, and simulated saliva. Most of these test solutions are commercially available and the formulae are well defined in test standards. For some tests, the compositions of the test solutions are altered to represent the worst-case scenario that the device may encounter. It is common to spike simulated saliva with hydrogen peroxide, fluoride, and lactic acid. Some test conditions may need to mimic an inflammatory condition, and for those cases, varying concentration of hydrogen peroxide is added to the test solution. For wear testing of articulating surfaces on orthopedic devices, the test solution is mostly composed of diluted fetal bovine serum (FBS), which mimics the lubricating properties of synovial fluid (McKellop et al. 1978; ASTM 2013a).

5.2.2 Mechanical Interactions

Mechanical interactions (fatigue, fretting, and wear) of metallic implants can also affect corrosion susceptibility. An oxide layer forms on the surface of passive alloys (e.g. chromium oxide for stainless steel, titanium oxide for nitinol), which acts as a protective layer against corrosion. Damage or disruption to this passive layer can either weaken the protective layer or directly expose the underlying metal to corrosion. For some time it was thought that fatigue (e.g. cyclic deformation or loading) could lead to fractures in the oxide layer and increase the corrosion susceptibility of metallic implants (2005). Industry experience and FDA research has shown that this is generally not the case and fatigue itself does not increase pitting corrosion susceptibility (Nagaraja et al. 2016b; Di Prima, Guiterrez, and Weaver 2017). However, the effect of dynamic loading on other corrosion mechanisms is not well understood; some initial works have shown an increase in metal ion release under dynamic loading, but whether it results from surface damage or a change in diffusion kinetics is unknown (Peitsch et al. 2007; Milheiro et al. 2012). Fretting and fretting corrosion can remove the protective oxide layer and over time prevent the formation of a new oxide layer. Initial research has shown that fretting does not necessarily increase pitting corrosion susceptibility (Siddiqui et al. 2016); however, fretting generates metal debris and changes the protective oxide layer, which can impact metal ion release. Metal debris from fretting and other wear mechanisms by themselves can have a significant effect on metal ion release rates even when the metallic implant has a low ion release rate from general corrosion. It is, therefore, important to understand the mechanical interactions a metallic device is expected to experience *in vivo* in order to determine the testing necessary to establish a reasonable assurance of safety.

5.2.3 Active Devices

Electrical stimulation is used as a therapy in cardiac, muscle, and neural devices. Among these, implantable cardiac electrical stimulators, such as defibrillators and pacemakers, have the largest patient base. Implantable electrical stimulators activate excitable tissue by passing electric current via electrodes placed next to the target tissue (Merrill, Bikson, and Jefferys 2005). Electrodes of implantable electrical stimulators may be made of Elgiloy® (Parsonnet et al. 1981), stainless steel (Scheiner, Polando, and Marsolais 1994), titanium nitride, iridium oxide, or platinum and platinum-iridium alloys. Platinum and platinum alloys are most commonly used.

Electrical stimulation is mediated either via non-Faradaic or Faradaic processes (Figure 2A). Non-Faradaic charge injection is associated with rapid changes in concentration of ions near the electrode surface without actual transfer of charge between electrode and solution. This process does not lead to changes in chemical composition in tissue near the implant or electrode and does not contribute to metal ion release. Alternatively, Faradaic processes involve actual transfer of electrons between electrode and solution that can lead to metal oxidation, electrode corrosion, and metal ion release (Brummer, McHardy, and Turner 1977; Black and Hannaker 1979; McHardy et al. 1980; Kumsa, Hudak, et al. 2016). While non-Faradaic stimulation is ideal in terms of minimizing ion release, these processes

are limited in the amount of charge that can be transferred. For most current stimulation device designs, the use of Faradaic processes is necessary to achieve desired functionality.

Platinum dissolution was long thought not to be a concern, so historically it has been the primary electrode material used in stimulation devices. However, recent clinical evidence of platinum electrode dissolution has been reported (Clark et al. 2014; Nadol et al. 2014; O'Malley et al. 2017). While the precise mechanism of platinum release (Figure 2A) is not well understood, evidence of electrode corrosion and release of platinum in both soluble and insoluble forms has been detected with a variety of analytical techniques (Figure 2B) (Brummer, McHardy, and Turner 1977; Black and Hannaker 1979; McHardy et al. 1980; Robblee et al. 1983; Shepherd and Clark 1991; Clark et al. 2014; Nadol et al. 2014; Seyyedi and Nadol Jr. 2014; Kumsa, Hudak, et al. 2016; Spiers et al. 2016). Based on the existing data, the degree of platinum release from an electrode during therapeutic electrical stimulation will be accelerated with an increase in amplitude of stimulation current, increase in stimulation frequency, and increase in a total time of stimulation therapy (Figure 2C). Additionally, parameters such as length of stimulation pulse, electrode geometry, and solution composition might also influence rate of platinum release (Robblee et al. 1980; Robblee et al. 1983; Shepherd and Clark 1991). While other electrode materials are used in device applications, data available on the relationships between stimulation parameters and dissolution susceptibility of these materials are far more limited.

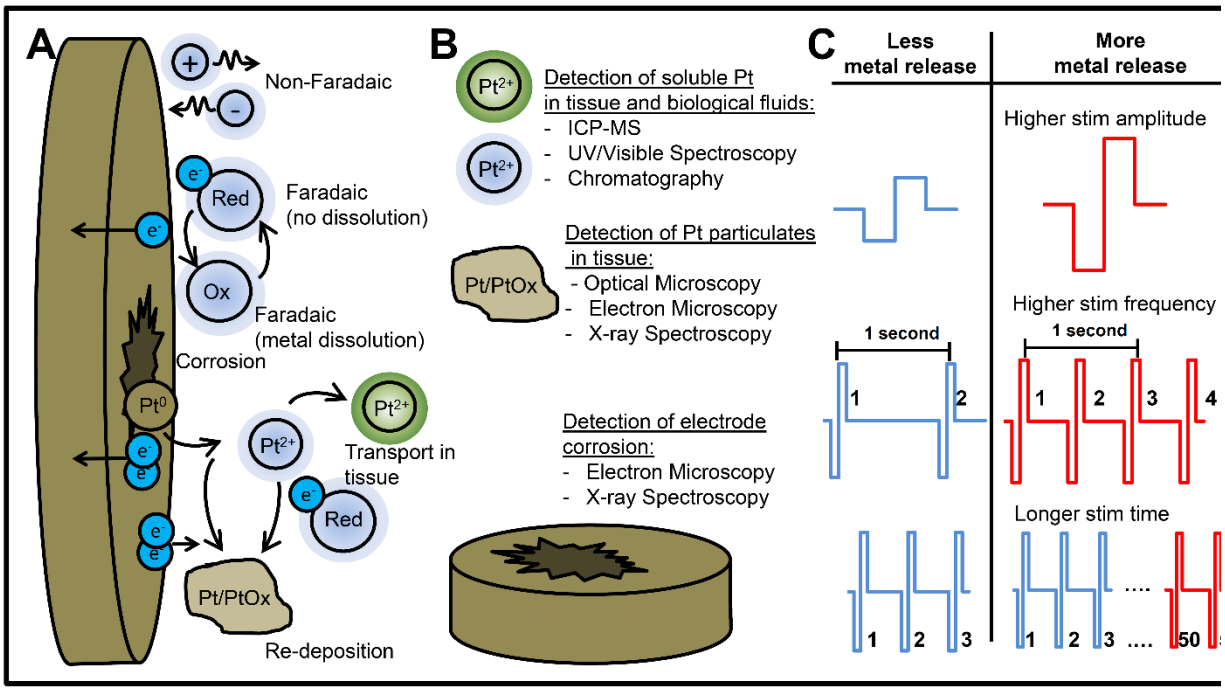

Figure 2: Platinum release from active implants during electrical stimulation. (A) Proposed mechanism of platinum release. (B) Analytical techniques used to detect electrode corrosion and platinum release. (C) Parameters of electrical stimulation that influence platinum release.[7]

[7] Figure created by Pavel Takmakov and released under Creative Commons 4.0 (CC BY 4.0) license

5.2.4 Processing

The effectiveness of an oxide layer as a protective barrier is a function of the oxide chemistry, thickness, and integrity. Oxide chemistry will dictate how inherently protective the oxide is as well as how well the oxide will adhere to the metal substrate. Oxide thickness will influence how flexible the oxide layer is (i.e., how prone it is to damage) and the chemistry of the metal may give rise to suboptimal intermetallic regions forming within the oxide layer, such as nickel-rich phases in nitinol. Metal ion release and corrosion can occur across the entire surface area of a device; therefore, an oxide layer that is uniform and defect-free provides more optimal protection. Generally, the most protective oxide layer is chemically stable, adheres well to the metal substrate, has no subsurface intermetallic layer, and is thin (~10 nm), uniform, and defect free.

The oxide layer can be modified through several surface finishing and passivation steps. These steps are typically performed at the end of the manufacturing process as high temperature processing (e.g., annealing, tempering, and shape setting) can increase the thickness of the oxide layer and reduce corrosion resistance. The surface finishing step serves to remove the existing oxide layer, any subsurface intermetallic layers, as well as gross manufacturing surface defects or damage. There are three common surface finishing techniques used for medical devices: chemical etching, mechanical polishing, and electropolishing. These can be used alone or in combination. Chemical etching involves soaking the device in a strong acid that selectively dissolves the layer between the metal substrate and the oxide layer. The oxide layer can then be removed by sonication (high frequency sound waves). Mechanical polishing utilizes an abrasive media to physically remove surface material including the oxide layer and any subsurface intermetallic layers from the device. Electropolishing involves submerging a device in a chemical solution (generally acidic) and applying a current to controllably erode the surface to remove the oxide layer or any subsurface intermetallic regions. Surface finishing often removes a significant amount of material to ensure a uniform and pristine surface for passivation. While passive metals will spontaneously form an oxide surface, the passivation process allows for a controlled growth of a new oxide layer after the surface finishing step. Passivation generally consists of submerging the metal device in acid for a controlled temperature and duration.

5.3 *IN VITRO* CORROSION TESTING

Because of the many confounding factors that influence the corrosion susceptibility, historical use of an alloy in medical devices is typically not sufficient to conclude that there are no concerns regarding corrosion for a specific device; therefore, it is important to conduct device specific testing to evaluate corrosion resistance in relevant physiologic and mechanical environments. *In vitro* testing is routinely conducted to evaluate the relative propensity for corrosion of a specific device through different possible mechanisms. In this section, we review these *in vitro* tests including when they are utilized, protocols, and typical results for commonly used implant alloys.

5.3.1 General Corrosion

To assess general corrosion/metal ion release, *in vitro* immersion testing is often conducted to quantify metal ion release over time under physiologically relevant conditions. This testing typically consists of placing the metallic device in a container filled with media representative of the implant environment and storing for a predetermined duration. At subsequent time intervals, the device is removed from the container and placed into a new container with fresh media. Once the device is removed, the media is sampled for chemical analysis using methods such as inductively coupled plasma mass spectrometry (ICP-MS). This testing is usually conducted for a sufficient duration to establish that ion release has reached steady-state or approached equilibrium, and the time intervals are selected to adequately capture the extent of any initial bolus release from the device. In addition to providing a framework for

comparing different alloys, designs, or manufacturing processes, immersion test data are used to estimate exposure as part of toxicological risk assessment (*e.g.,* per ISO 10993-17). The American Standard of Testing and Materials (ASTM) recently published ASTM F3306 "Standard Test Method for Ion Release Evaluation of Medical Implants" that describes test methods to assess ion release from metallic implants (ASTM 2019).

There are several factors that need to be considered when conducting this testing and interpreting the results. For example, the ratio of device surface area to media volume is an important consideration to ensure that metal ion concentrations do not approach solubility limits yet are sufficiently high enough to be quantified using a suitable analytical method. Container choice is also critical because metal ions tend to adsorb onto some container materials leading to an underestimate of the extent of release. Further, precipitation reactions can also result in a substantive loss of released ions from the solution. Thus, test protocols are typically validated using calibration solutions of known concentration and assessing if metal ions are lost during immersion. It is important to note that immersion testing does not completely simulate *in vivo* conditions where cells, proteins, mechanical loading, and other factors that can impact ion release are not replicated; therefore, the clinical applicability of the results are uncertain.

There have been numerous results of metal ion release testing reported in the literature. For passive device alloys, the clear majority of efforts have focused on nitinol because the processing of this alloy can have significant impact on nickel ion release. In fact, a range of reported nickel release rates for nitinol processed with different conditions spans three orders of magnitude. On average, acute release varied from 6.0 to 1300 ng/cm^2/day in PBS, for well-passivated (electropolished) and thick oxide materials, respectively (Sullivan et al. 2015). The rates diminished to 0.2 and 69 ng/cm^2/day, respectively, after 60 days. While there have been several studies on ion release from nitinol devices, these values are a good representation of the potential *in vitro* release rates anticipated for this material under idealized conditions. The effect of the pH of the immersion media on nickel release from nitinol has also been characterized (Okazaki and Goth 2008; Capoşi, Prodana, and Ioniţă 2011). Okazaki et al. (2008) observed relatively consistent nickel release for mechanically polished nitinol below 200 ng/cm^2 over 7 days for pH in the range of 3-7.4, using a range of solutions including: PBS, calf serum, α-medium, NaCl+HCl solutions, artificial saliva, Ringer's solution, lactic acid, and L-cysteine. However, nickel release was found to dramatically change below a pH of 3, increasing by nearly two orders of magnitude as the pH of the media fell below 2. Ion release has also been characterized from other common implant alloys, albeit to a lesser extent. For example, studies have shown that cobalt-chromium and stainless steel alloys tend to release less nickel than nitinol in Hank's solution when the surface finishing processes are similar (Trépanier et al. 2000). It has also been demonstrated that, in physiologically relevant media, mechanically polished cobalt-chromium alloys release 300-600 ng/cm^2 of cobalt over the first week, whereas chromium release was found to be lower than 15 ng/cm^2 over the same time frame (Okazaki and Goth 2008). In this same study, the total amount of metal ions released from a variety of mechanically polished stainless steels was also found in the same range 300-600 ng/cm^2 after one week, which primarily consisted of iron and cobalt.

5.3.2 General Corrosion - Active Implants

Assessment of corrosion for active implants – devices with an electrical current - *in vitro* can be performed using the same techniques as for passive implants described above. For example, ICP-MS is used to detect the release of platinum from electrodes during electrical stimulation (Brummer, McHardy, and Turner 1977; Black and Hannaker 1979; McHardy et al. 1980; Kumsa, Hudak, et al. 2016). Kumsa et al. (2016) reported a maximum of 2.2 µg/cm^2/h (Kumsa, Hudak, et al. 2016) whereas Robblee et al. (1980) reported a maximum of 7.8 µg/cm^2/h (Robblee et al. 1980) at a larger charge injection level than Kumsa et al. (2016). Robblee et al. (1983) also found a maximum of 3.9 µg/cm^2/h of Pt *in vivo*.

Robblee et al. (1983) estimated a linear etching rate of 1.8 nm/h *in vivo* under the assumption of uniform dissolution (Robblee et al. 1983). Electrode integrity and evidence of corrosion can be assessed with scanning electron microscopy (SEM) (Shepherd et al. 1985; Siegfried and Rea 1988), atomic force microscopy (AFM) (Mailley et al. 2004), electron dispersion spectroscopy (EDS) (Wang, Petrossians, and Weiland 2014), or x-ray photoelectron spectroscopy (XPS) (Takmakov et al. 2010). However, since for active implants a significant potential is applied to an electrode during electrical stimulation, advanced electrochemical techniques such as cyclic voltammetry (Bard and Faulkner 2000) provide more thorough understanding of electrode corrosion (Kumsa, Hudak, et al. 2016; Kumsa, Bhadra, et al. 2016). Additionally, since platinum is the most frequently used electrode material, other analytical techniques such as UV/Vis spectroscopy (Brummer, McHardy, and Turner 1977) and ion selective chromatography (Nachtigall, Artelt, and Wünsch 1997) are used to establish whether Pt (II) or Pt (IV) is released from the electrode during neurostimulation. Clinical observation of platinum electrode dissolution is very recent and not well known by medical device manufacturers. There is only one comprehensive standard for neuromodulation devices, ANSI/AAMI CI86:2017 "Cochlear implant systems: Requirements for safety, functional verification, labeling and reliability reporting", which has been released and addresses this issue very briefly (AAMI 2017). Because Pt dissolution can occur during electrical stimulation, it is important to consider the dissolution behavior of thin film Pt electrodes prior to clinical use.

5.3.3 Pitting Corrosion

The most common nonclinical method to evaluate pitting corrosion is ASTM standard test method F2129 "Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices" (ASTM 2017). This standard test method assesses pitting corrosion potential of medical devices *in vitro*. This test method provides the voltage (breakdown potential) required to initiate pitting on the device surface. Although not representative of *in vivo* conditions, this accelerated test provides a detailed method to determine corrosion behavior of devices relatively quickly and consistently. In brief, this test method involves immersing the device in de-aerated electrolyte solution and subjecting the device to a voltage scan at a predetermined scan rate. Typically, the voltage scan starts after the device has been immersed in the electrolyte for an hour. The current density is monitored during the voltage scan and pitting corrosion begins when there is a sudden increase in the current density. The voltage at this sudden increase is defined as the breakdown potential and is a measure of pitting corrosion resistance. The voltage scan is reversed at typically 800-1000 mV and scanned in the negative direction until it reaches the rest potential. If breakdown occurs, a visual inspection is recommended to characterize the locations and extent of pitting. The resulting voltage vs. log (current density) curve aids in understanding the electrochemical behavior of the material used in the device.

An acceptance criteria for this test was proposed based primarily on expected electrical potentials *in vivo* (Corbett 2004; Rosenbloom and Corbett 2007). These articles recommended that implants with a breakdown potential exceeding 600 mV have acceptable corrosion resistance, while potentials below 300 mV are unacceptable. However, there is considerable debate within the medical device community on the use of these acceptance criteria and their clinical relevance (Pound 2006; Eiselstein et al. 2009). The inability to generate universal acceptance criteria for nonclinical corrosion testing is due to difficulties in observing corrosion clinically and correlating this with *in vitro* corrosion tests. An FDA workshop was held in 2012 to better understand typical corrosion results for cardiovascular devices (Nagaraja et al. 2016a). For nitinol devices, industry respondents reported breakdown potentials ranging from -100 mV to no breakdown (i.e., over 800 mV), with a median breakdown potential of 388 mV. Stainless steel and cobalt-chromium alloys also had a wide range of breakdown potentials (26 mV to no breakdown over 800 mV), with median breakdown potentials generally higher compared with nitinol

devices. The median breakdown potentials for stainless steel and cobalt-chromium-based devices were 658 mV and 654 mV, respectively.

5.3.4 Crevice Corrosion

Although there are FDA recognized test methods for assessing crevice corrosion for a metal surface (*e.g.*, ASTM F746 "Standard Test Method for Pitting or Crevice Corrosion of Metallic Surgical Implant Materials"), these test methods were developed to screen candidate metallic materials, not device designs. Therefore, most medical device manufacturers do not use these test standards to evaluate the susceptibility of their medical device designs to crevice corrosion. However, some device manufacturers use ASTM F2129 to evaluate their designs for crevice corrosion susceptibility.

ASTM F746 involves testing a cylindrical rod of the metallic material with a teflon washer to create a crevice of known geometry (ASTM 2014a). This crevice is potentiostatically held above the breakdown potential to induce corrosion and then systematically lowered until the repassivation (oxide reforms) potential is reached. In most orthopedic devices, the crevices formed are between modular metallic interfaces, which this test method does not replicate. Additionally, these crevices experience complex loads and micromotion, which can amplify crevice corrosion. Hence, most device manufacturers look for crevice corrosion within modular junctions after they have performed fatigue testing. At present, most of the cardiovascular devices are not specifically tested for crevice corrosion susceptibility, but rather for its general local corrosion susceptibility. ASTM F2129 test method is typically used to determine if corrosion occurs when crevices are present.

Research studies have shown that stainless steel alloys are more prone to crevice corrosion as compared to other alloys (Serhan et al. 2004). A comparison between ASTM F2129 and ASTM F746 has shown that crevices formed between overlapped stents made from nitinol and stainless steel are prone to crevice corrosion when wear is involved (Trépanier et al. 2008). Crevice corrosion was also reported in stainless steel fracture fixation plates. ASTM F2129 and ASTM F746 testing illustrated that stainless steel and cobalt-chromium alloys are prone to crevice corrosion, however, the corrosion damage was more severe in stainless steel (Reclaru et al. 2002). Cobalt-chromium samples exhibited discoloration in locations where a crevice was present.

5.3.5 Fretting

There are no general standard test methods for fretting (wear) corrosion of medical devices. However, *in vitro* assessments of fretting for cardiovascular devices are usually performed after fatigue testing to analyze whether the passive oxide layer was disrupted sufficiently to induce localized corrosion and/or fatigue cracking. In orthopedic devices, there are recognized standards such as ASTM F1875 "Standard Practice for Fretting Corrosion Testing of Modular Implant Interfaces: Hip-Femoral Head- Bore and Cone Taper Interface." This standard has two suggested methods. The first method involves subjecting the device to long-term fatigue testing and evaluating the device for damage resulting from fretting or corrosion by measuring the corrosion products generated at the bore and cone interfaces. The second method involves electrochemically monitoring the device for current as the device is subjected to fatigue. The intent of the second method is not to produce fretting corrosion damage, but rather to evaluate if design changes impact fretting susceptibility (ASTM 2014b).

5.3.6 Galvanic Corrosion

For devices that contain different alloys in direct (electrical) contact, the acceleration of corrosion due to galvanic interactions becomes a concern. In a galvanic couple, the more noble alloy (i.e., the one with higher electron affinity) acts as the cathode, in which corrosion is inhibited, and the less noble alloy acts as the anode, in which corrosion is accelerated. The rate of galvanic corrosion depends on the potential

difference between the two alloys and the surface area ratio. Specifically, larger potential differences and cathode to anode surface area ratios give rise to higher galvanic currents. Thus, concerns associated with galvanic corrosion often can be mitigated through careful device design. However, this is not always possible, and some medical conditions require treatment with multiple devices that are in direct contact once implanted and can be comprised of different materials (*e.g.*, overlapping stents). In these scenarios, it is important to characterize the magnitude of the galvanic interactions.

Galvanic corrosion is typically assessed by first preparing the alloys present in the couple as individual electrodes. The electrodes are subsequently immersed in a physiologically relevant medium within a polarization cell and the galvanic current and coupled potential are monitored over time. The test typically continues for a predetermined time or until steady state conditions are reached. Medical device-specific considerations for this type of testing are detailed in ASTM F3044 (ASTM 2014b). Because many devices contain dissimilar components that cannot be readily separated, it is often necessary to mask off opposing components on separate devices for testing or to use representative samples for one or both components. In these situations, it is critical that the relative cathode to anode surface area on the finished device is maintained.

Results of galvanic corrosion testing for commonly used device alloys reported in the literature focus primarily on couples with comparable surface area (Venugopalan and Trépanier 2000; Carroll and Kelly 2003; Pound 2016). While these tests are conducted in different solutions and different surface preparations are used for the same alloys across studies, some common trends in the data emerge. For example, nitinol usually behaves as the anode, suggesting that it is the less noble, when coupled to other common passive device alloys, such as stainless steels and cobalt-chromium alloys. However, because these alloys lie relatively close to one other in the galvanic series, the resulting galvanic currents tend to be small, in the range of 1-100 nA/cm^2. Cobalt-chromium alloys and stainless steels favor the lower and upper portions of this range, respectively. The observed currents are of the same order as the currents for well-passivated uncoupled materials, which suggest significant acceleration of corrosion due to galvanic interactions should not be commonplace with these alloys. As expected, when nitinol is coupled to more noble metals, such as Pt, a considerable increase in galvanic current, in the range of 100-1000 nA/cm^2, has been reported. In fact, the corresponding potential shift due to coupling with Pt has been observed to exceed the breakdown potential in mechanically polished nitinol (Pound 2016). However, it is important to note that in most medical device applications that couple noble metals and passive alloys such as nitinol, the surface area of the noble metal is relatively small, thereby significantly reducing the effect of galvanic interactions.

5.4 *IN VIVO* CORROSION

The *in vitro* test methods described above can provide significant insight into the corrosion susceptibility of a given device. However, they are typically conducted under idealized and/or hyper-physiological conditions. Thus, while these tests enable comparisons between devices to be readily made, the extent to which *in vitro* performance correlates to corrosion behavior *in vivo* remains unclear. This is primarily due to the scarcity of relevant *in vivo* data. In general, the electrochemical processes that drive corrosion lead to both dissolution of metal (as ions) as well as surface deposition (which can be called a corrosion product). Additionally, based on the solubility of the dissolved ions, it is possible for the ions to precipitate out to form additional corrosion products. The surface deposition products are localized to areas near the corrosion location, corrosion precipitates are generally found on the device or in adjacent tissue, while the dissolved ions can be found systemically. The spread of corrosion products throughout the body make definitive corrosion product studies a challenge; most rely on analyzing the surface deposited/precipitated products while others include local tissue response. Below we review studies

that have characterized *in vivo* corrosion of cardiovascular, orthopedic, and active devices. Potential (sub)clinical consequences of these observations are discussed in Sections 6 and 7. This section concludes with a discussion of the prospects for establishing *in vitro* to *in vivo* correlations for corrosion and information on how computational modeling may facilitate their development.

5.4.1 Corrosion in Cardiovascular Devices

The extent of patient exposure to corrosion by-products has been characterized in a limited number of cases for cardiovascular devices. Assessment of systemic exposure to corrosion by-products is typically limited to evaluating serum and urine levels of metal ions, due to the relative ease of measurement. For example, elevated serum and urine levels of nickel have been reported in patients receiving certain nitinol septal occluders (Ries et al. 2003; Burian et al. 2006), where serum concentrations as high as 6 μg/L were found and urine levels reached approximately 20 μg/L, compared to baseline values, which are typically less than 1.1 and 4.4 μg/L in serum and urine, respectively (Saravanabhavan et al. 2016). However, these maxima were observed 2-4 weeks after implantation and the levels returned to within normal range after a few months. Localized corrosion by-products in stainless steel and nitinol cardiovascular stents have also been previously characterized (Halwani et al. 2010). The authors found elevated levels of nickel and chromium ions in arterial tissue surrounding stainless steel stents. Elevated levels of nickel and titanium ions were also observed in tissue surrounding nitinol stents. Recent research (Nagaraja et al. 2018) investigated whether nickel ions were elevated systemically or in local tissue due to corrosion in nitinol stents. While no increase in nickel ion levels in blood or urine were observed in miniature swine 6 months after implantation, there was evidence of increased nickel levels in local arterial tissue for corroded stents. Although the clinical ramifications of corrosion by-products in local vasculature are unclear, corrosion by-products have been thought to increase the risk of in-stent restenosis (re-narrowing) (Halwani et al. 2010).

5.4.2 Corrosion in Orthopedic Devices

Exposure to corrosion by-products has also been quantified from orthopedic devices after implantation. Concentrations of serum nickel, as well as chromium, have been reported in patients after implantation with stainless steel spinal implants (Kim et al. 2005) over long time frames. Both elevated nickel (~7 μg/L) and chromium (~9 μg/L) were found after 6 months, which was the earliest recorded time point. While chromium levels returned to the normal range after about 2 years, nickel concentrations above the normal range were still found in some patients after 13 years (~1.5-2 μg/L). Nickel and chromium levels in both serum and urine have also been assessed in patients implanted with stainless steel spinal implants with and without evidence of macroscopic corrosion 13-15 years after implantation (del Rio, Beguiristain, and Duart 2007). Even in the absence of macroscopic corrosion, elevated levels of both elements were observed after more than a decade following surgery. When macroscopic corrosion was evident, nickel was found well outside the limits of the normal range (up to 0.1 μg/L serum and up to 4 μg/L urine), with maxima of 9 and 300 μg/L in serum and urine, respectively. The reported chromium levels were similarly quite high (normal upper limit: 0.16 μg/L serum and 0.22 μg/L urine), with a maximum serum level of 33 μg/L and up to 97 μg/L found in urine.

Conversely, in patients receiving cobalt-chromium alloy arthroplasty prostheses, no discernible increase in chromium was found in the serum and urine while only slightly enhanced levels of cobalt were observed 2-120 weeks after surgery (Sunderman et al. 1989). Local corrosion by-products from metal-on-metal modular hips have also been investigated. The results suggest that the bulk of corrosion products found are due to chromium ions precipitating out of synovial fluid, with the more soluble cobalt ions free to spread further. Analysis of local tissue has shown a wide variation in the amount of metal and that there can be greater than 500 ng/g of cobalt, titanium, and iron present with lesser

amounts of chromium and nickel (Meyer et al. 2012). This same work also illustrated that the metal content was highest in the capsule and the bursa. Other analysis showed much higher maxima of metals in the local tissue; cobalt 187 μg/g, chromium 752.6 μg/g, and nickel 3.99 μg/g (Lohmann et al. 2013). However, these analyses are unable to differentiate if this is from metallic wear debris, corrosion products, or incorporation of metallic ions. For systemic exposure, studies have shown serum levels of 0.58 to 190 μg/L of chromium and 0.38 to 228 μg/L of cobalt (Langton et al. 2009). For hips, there is a correlation between systemic metal ion levels and prosthetic size and positioning (De Haan et al. 2008; Langton et al. 2008), indicating that wear is a significant factor in systemic metal ion exposure in total hip replacements. Normal range of chromium in serum is 0.10 to 0.16 μg/L while for cobalt it is 0.08 to 0.5 μg/L (Sciences 2012).

5.4.3 Corrosion in Active Devices

Animal studies provide extensive evidence on corrosion of platinum electrodes. This includesg SEM observations of electrode pitting (Shepherd et al. 1985) and presence of soluble platinum species in tissue (Robblee et al. 1983; Shepherd et al. 1985). Additionally, there has been gross histopathology evidence of deposition of platinum particulates in local tissue (Bernstein et al. 1977). Clinical evidence of platinum release for cardiac devices includes results of SEM examination of cardiac leads (Parsonnet et al. 1981) that showed signs of corrosion. In case of neuromodulation devices, post-mortem studies of cochlear implants patients revealed platinum containing particles in tissue adjacent to the electrodes (Clark et al. 2014; Nadol et al. 2014; Spiers et al. 2016; O'Malley et al. 2017). There are no clinical reports documenting platinum release for other neuromodulation devices, but it does not mean that this process is absent for these cases. Clinical implication of platinum release is unknown. Some soluble platinum salts are known to be toxic (Agnew et al. 1977; Kovach et al. 2016); however, it is not well understood what particular form of platinum is released from the electrodes during neurostimulation and whether it possesses any unique health risks.

5.4.4 Correlation to *In Vitro* Testing

In general, quantitative links between the *in vitro* test results described in 5.3 and *in vivo* behavior have not been established. However, available data do suggest there are at least qualitative consistencies. For example, *in vitro* testing reported on certain septal occluders suggests relatively low breakdown potentials (80 mV) (Kong et al. 2002) and high nickel release (Verma et al. 2015) compared to other nitinol devices. *In vivo* observations for these devices suggest that minor pitting may occur (Kong et al. 2002) with elevated nickel levels in both serum and urine (Ries et al. 2003; Burian et al. 2006). Similarly, *in vitro* immersion testing of cobalt-chromium alloys suggests relatively low levels of ion release that is dominated by cobalt (Okazaki and Goth 2008). Again, these *in vitro* observations are consistent with serum and urine ion levels measured in patients with cobalt-chromium alloy arthroplasty prostheses (Sunderman et al. 1989). While causal relationships between *in vitro* and *in vivo* response such as these can be suggested, any quantitative links between bench test results and patient exposure to corrosion products remain largely unknown. Therefore, uncertainty in patient exposure is one of the largest knowledge gaps to establishing patient risk associated with corrosion products generated by metallic implants.

Although linking the results of *in vitro* testing to *in vivo* outcomes presents formidable challenges, ongoing research is attempting to address some of these unknowns. For example, recent efforts using animal models have shown that the results of *in vitro* pitting corrosion testing can be quantitatively linked to the propensity for pitting *in vivo* (Sullivan et al. 2017). In the same study, local tissue concentrations of nickel adjacent to the implant site of nitinol stents were closely correlated with the results of *in vitro* nickel release testing. While animal models can provide significant insight into the

relationship between *in vitro* corrosion testing and *in vivo* exposure to corrosion products, these studies can be difficult and prohibitively costly and time-consuming. As an alternative, modeling and simulation tools represent a promising and relatively easy way to potentially establish these relationships quantitatively. For example, toxicokinetic models can link *in vivo* metal ion release to easily measured clinical parameters, such as serum or urine ion concentrations, enabling *in vivo* exposure inferred from these measurements to be compared directly to the results of *in vitro* testing (Saylor et al. 2016). While toxicokinetic models can be used to predict systemic exposure due to the presence of a metallic implant, they are not sufficiently refined to resolve accumulation and dispersion of metal ions in tissue local to the implant. However, physics-based models of the device and local tissue environment can be used to further refine systemic models (Saylor et al. 2018). The largest drawback to employing computational models to accurately predict exposure to corrosion products is the need for validated model parameters.

Establishing *in vitro* to *in vivo* correlations for metallic implant corrosion will likely require a combination of computational modeling and *in vitro*, *ex vivo*, and *in vivo* testing as well as clinical studies to inform and validate the model predictions.

6 SUBCLINICAL RESPONSE TO METAL IMPLANTS

A patient's overall response to a metal implant consists of responses both at the implant location as well as systemically. Immune cells are primarily responsible for these responses. Immunological cell responses are either innate (requiring no prior exposure) or adaptive (acquired only after an antigen is encountered). Both cell responses are involved with adverse reactions associated with metal implants. Such responses can be observed histologically, however this analysis is only possible when there is a biopsy of the tissue or device removal. Metal debris from implants, in the form of ions and particulates, has various effects. Metal debris may damage cells and may activate specific immune and inflammatory pathways, sometimes leading to patient sensitization. Particles are taken up by macrophages, which can lead to inflammatory and tissue-destructive reactions of various degrees. The cellular uptake of particles by macrophages can also lead to additional ion release, causing a positive feedback loop. Specific local tissue responses depend on the device or biomaterial and peri-implant tissue type as well as patient-related characteristics. Further research is needed to understand the underlying molecular mechanisms. Understanding the underlying molecular mechanisms is the first step to develop pre-operative screening to distinguish patients at greater risk for adverse reactions. It is also essential for identifying clinically-detectable signs that can predict post-operative metal implant failure.

6.1. INTRODUCTION

The purpose of this section is to present immune and other biological responses which can be elicited by the presence of various implantable/insertable materials and devices as well as their degradation products in the human body (see Section 5). For the purposes of this section, we have defined

"subclinical" as biological processes that are considered underlying mechanisms for clinically-manifested outcomes (see Section 7).

Implants have been shown to elicit intrinsic responses which are coupled to molecular and cellular pathways that help determine the success or failure of an implant in a given patient. Underlying maladaptive responses may resemble "normal" responses, depending on a variety of contextual dimensions. Robust homeostatic mechanisms are intrinsically integrated into these networks, critical to the resolution of inflammation in successful, stable implants. Perturbations in one pathway may disturb other responses in the network, leading to adverse outcomes through indirect mechanisms.

Specialized immune cells and host tissues are critical mediators of the implant-host interface. While many pathways and mechanisms are ubiquitous and shared across device types and implant sites (Section 6.1.1 and 6.3), others may be selectively important or even sequestered to certain sites, devices, and applications (Section 6.4).

A more comprehensive understanding of the fundamental inflammatory and immunologic biology of responses to metals would facilitate identification of clinically useful signatures that are necessary for developing diagnostic or prognostic tests for patients with metal implants.

6.1 WOUND HEALING

Implanted devices that are not surface contacting (e.g., mucosal) are introduced via purposeful wounding of native tissue to gain access to or prepare an implantation site. This activates wound healing, which is a highly regulated, deeply conserved program induced in response to tissue damage caused by trauma and infection. Cell-cell contact, and soluble factors orchestrate complex interactions between numerous pathways. Initial clotting is coupled to inflammatory pathways including leukocyte influx, cellular turnover, angiogenesis, and matrix remodeling. Critical checkpoints in early wound healing determine later outcomes: resolution or chronic inflammation (Gurtner et al. 2008). When foreign/implanted materials are present at the wound site, outcomes are influenced by the nature of the resulting foreign body reaction (FBR) (see Section 6.2.2).

Immediately following tissue damage, the intrinsic coagulation pathway is activated, initiating clot formation. Platelet activation through interactions with collagen and fibrin elicits platelet degranulation, (Furie and Furie 2004). Early neutrophil recruitment, within the first three days, leads to further amplification of inflammatory pathways. Neutrophils at the wound site are supplanted by macrophages within days, differentiated *in situ* largely from monocytes recruited from circulation.

In the next phase, between days 2-10, granulation tissue is generated by deposition of extracellular matrix (ECM) by fibroblasts and neovascularization by proliferating endothelia (Krafts 2010). Fibroblast production of types I and III collagens are of critical importance to ECM stability in the healing wound; fibroblast-derived glycosaminoglycans, elastic fibers, and other glycoproteins modulate the mechanical and structural properties of the developing ECM (Chiquet 1999). Myofibroblasts represent an even further specialized subset of fibroblasts enriched for expression of smooth muscle actin, facilitating contraction of the resulting scar tissue (Hinz 2016). Platelet-derived growth factors (PDGFs), transforming growth factor beta (TGFβ), fibroblast growth factors (FGFs), and vascular endothelial growth factors (VEGFs) also promote proliferation of endothelial cells, intrinsically linking fibrogenic with angiogenic signals (Tonnesen, Feng, and Clark 2000; Wong and Crawford 2013). Highly specific and

potent VEGFs, the angiopoietins, are effectively induced by hypoxia-inducible factor 1-alpha (HIF1α), a key sensor of oxygen tension and hypoxic stress in the wound environment (Yamakawa et al. 2003; Ahluwalia and Tarnawski 2012). HIF1α modulates the balance of tissue remodeling, controlling expression of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinase (TIMPs), in a manner that is responsive to metal particles (Wan et al. 2011). The hypoxic stress response also initiates an angiogenic program, whereby healing tissues promote the outgrowth and expansion of neo-vascular beds through coordinated signals from macrophages, endothelia, and platelets (Knighton et al. 1983; Pugh and Ratcliffe 2003). Angiogenic growth is sensitive to ECM and clot through endothelial expression of laminins and integrins (Li, Zhang, and Kirsner 2003; Laurens, Koolwijk, and de Maat 2006).

Extensive crosstalk between these many cell types and signaling pathways constitute a carefully orchestrated network regulating healing processes. Macrophages are prime sources of TGFβ, a family of cytokines central to the orchestration of fibrogenesis and tissue remodeling (Kyriakides and Maclauchlan 2009; Sweetwyne and Murphy-Ullrich 2012; Kim, Sheppard, and Chapman 2018). Macrophage responses to instructive signals can drive pro-fibrotic and pro-angiogenic transcriptional and metabolic programs, described as M2 or "alternatively-activated" polarization (Jetten et al. 2014; Jha et al. 2015). Cell-cell contact signaling between fibroblasts and inflammatory cells, including M1 macrophages, also may trigger the release of pro-inflammatory mediators such as IL-6 and IL-8, amplifying inflammation (Zhang et al. 1998).

Wound healing processes can be complicated by metallic debris resulting from wear or corrosion, including metal ions. Delayed or excessive healing can be features associated with long-term adverse outcomes in a variety of implant settings. Endothelial responses to metal oxides enhance angiogenesis in a manner that is also coupled to leukocyte recruitment (Liu et al. 2009; Ninomiya et al. 2013; Tan et al. 2016). Maladaptive orchestration of angiogenesis, inflammation, and inflammatory leukocyte trafficking may underlie the pathogenesis of an adverse local tissue reaction (ALTR) (Davies et al. 2005; Willert et al. 2005; Campbell et al. 2010).

6.1.1 **Foreign Body Response (FBR)**

Wound healing and other host responses to metal implants involve innate immune mechanisms that are collectively described as the foreign body response (FBR). The FBR can be characterized as a coordinated cascade of inflammatory and cellular mechanisms that are critical to acceptance of the implanted device (Christo et al. 2015). Abnormal immune responses may lead to adverse local tissue reactions (ALTR) including osteolysis, necrosis, pseudotumor formation, tissue granulation, and fibrous capsule contractions (Major et al. 2015).

Most immediately following implantation, host protein adsorption to the implant surface initiates the FBR. Injury to host tissues is rapidly followed by activation of coagulation and complement pathways and adsorption of proteins including fibrinogen, fibronectin, vitronectin, and globulins to the implant surface; this heterogenous mixture of stress response proteins and extracellular matrix components forms a matrix on and around the implant (Anderson, Rodriguez, and Chang 2008). With time, recruitment of immune cells, most notably macrophages, leads to the formation of foreign body giant cells (FBGCs) and fibrous encapsulation of the implant (Moore and Kyriakides 2015).

Early events in the response to an implant and, by extension, minor perturbations from stereotyped programs can therefore have significant consequences further downstream in the concerted response.

As with other kinds of biological cascade reactions, perturbations from the stereotypical, canonical program may arise from crosstalk between multiple pathways, as well as bystander inflammation and immunity at distant sites, unrelated to the implant. This rapid innate response equilibrates to steady state within one to two weeks following implantation. Failure to resolve acute inflammation proceeds to chronic inflammation which may precipitate ALTR and potential implant failure (Gibon et al. 2017; Klopfleisch and Jung 2017).

6.2. Innate Immune Responses To Metal Implants

Innate immune mechanisms are critical first responders to both microbial and toxicological insults. This characteristic holds true for immune responses to metal implants. Multiple factors influence the nature and magnitude of the innate response to metal implants, downstream inflammatory and immune responses, and the ultimate success or failure of the implanted device. The elemental composition; physical, chemical form (i.e., ion versus particulate), structural form; and amount of metal exposure may influence the nature of the innate immune response elicited following implantation. Location- or tissue-specific physiology and immunology may also provide numerous complicating factors, as well as the timing and course of implantation and implant-directed responses. The typical response to metal implants is characterized by rapid inflammation and innate immune response that equilibrates to steady state within one to two weeks following implantation. This resolution is critical to limiting tissue pathology and precluding subsequent implant failure.

6.2.1. Innate Immune Recognition of Metals

Recognition and uptake of metal debris initiates multiple inflammatory pathways including the inflammasome and pattern recognition receptor (PRR) pathways (Goodman, Konttinen, and Takagi 2014). While hematopoietic-origin leukocytes are enriched and specialized for these pathways, signals derived from injury of non-hematopoietic host tissues are also important, bridging immediate injury to tissues with early inflammatory and innate immune responses. The importance of signals derived from host tissues in providing impetus to initial inflammatory and innate immune responses undergirds the identity of these signals as “alarmins” or “danger”-associated molecular patterns (DAMPs) (Schaefer 2014; Rider et al. 2017).

The NALP3 (also known as NLRP3, CIAS1) inflammasome pathway comprises a multiprotein complex containing NALP3 and ASC, responsible for the activation of intracellular enzymes that lead to the production of inflammatory cytokines from immune cells, including IL1β and IL18 through activation of caspase 1 (Dostert et al. 2008). The NALP3 inflammasome is a primary sensing mechanism by which metal debris, both ions and particulates, induce the secretion of pro-inflammatory cytokines and recruit myeloid-lineage cells. Along with other types of implant related debris, metal debris was shown to activate the NALP3 inflammasome which is implicated in inflammatory processes such as osteolysis (St Pierre et al. 2010; Burton et al. 2013). Triggering of the NALP3 inflammasome by varying sizes and forms of metal debris may underlie divergent features of local inflammatory features at different device-tissue interfaces (Caicedo et al. 2009; Cobelli et al. 2011; Konttinen et al. 2014; Reddy et al. 2014; Scharf et al. 2014).

Pattern recognition receptors, exemplified by Toll-like receptor 4 (TLR4), also serve as critical triggers of inflammation following recognition of endogenous "alarmin" molecules released by injured tissues including heat-shock proteins, biglycan fragments, and heparan sulfates among others (Cobelli et al. 2011). Metal ions and particulates have been shown to directly activate TLR4, promoting local inflammation and tissue remodeling through driving NFκB-mediated cytokine production (Schmidt et al. 2010; Raghavan et al. 2012; Burton et al. 2013; Potnis, Dutta, and Wood 2013; Tyson-Capper et al. 2013; Konttinen et al. 2014; Lawrence et al. 2014; Lawrence et al. 2016; Samelko et al. 2017). In addition to TLR4, enriched expression of type A scavenger receptor (SR-A), interleukin-33 (IL-33), and integrin adhesion molecules on myeloid lineage cell types further couples sensing of metals and metal-induced tissue injury to endogenous wound healing responses (Kzhyshkowska et al. 2015).

Release of alarm signals from injured host tissues couple initial implantation to immediate inflammatory and innate immune responses; however, ongoing, persistent responses to implant-derived metal debris may also continue to modulate these inflammatory and immunogenic signals. Metal particles or ions can induce the apoptosis or necrosis of cells, including responding leukocytes (Peters et al. 2001; Catelas et al. 2003; Huk et al. 2004; Caicedo et al. 2008; Gill et al. 2012; Posada et al. 2014; VanOs et al. 2014; Posada, Tate, and Grant 2015). Sensing of physical and chemical characteristics of metal debris may determine apoptotic or necrotic programming in the context of other inflammatory microenvironmental signals, tuning further inflammatory signaling (Rosario et al. 2016). Tissue injury, presenting as necrosis in association with failed or compromised implants may perpetuate these maladaptive pathways (Grammatopoulos et al. 2016).

Altogether, these findings underscore that early, innate sensing of metallic implants and debris can be performed by multiple pathways – both direct (e.g. receptor recognition of metal ions, particulates, or surfaces) and indirect (e.g. recognition of alarmins released by tissue injury) (Samelko et al. 2016). These multiple mechanisms may comprise critically decisive determinants for the success or failure of the implant, and other downstream adverse events.

6.2.2. Innate Cellular Responses to Metals

Central to the FBR is the predominant infiltration of peri-implant tissues by macrophages – phagocytic cells specialized for defense against microbial pathogens, scavenging damaged tissue, and wound healing. As sentinels of innate immunity, macrophages express a wide range of PRRs. Triggering of PRRs expressed on macrophages elicits pro-inflammatory responses that are important for antimicrobial activity, profibrotic remodeling, induction of adaptive immunity, scavenging, and subsequent tissue repair (Mantovani et al. 2013; Wynn and Vannella 2016).

Macrophages are consistently present in significant numbers in tissues surrounding implants, particularly in cases of failure (Mahendra et al. 2009; Paukkeri, Korhonen, Hamalainen, et al. 2016). Macrophages and monocyte precursors are recruited to the implantation site by chemoattractants and growth factors including transforming growth factor (TGFβ), platelet-derived growth factor (PDGF), CXCL4/PF4, Leukotriene B4 (LTB4), and complement fragments (Anderson, Rodriguez, and Chang 2008). Macrophages at the implant site can be activated by metal debris and DAMPs released upon tissue injury and cell death, which signal through the NALP3 inflammasome and TLR pathways, leading to the production of pro-inflammatory cytokines, including IL1β, IL6, IL18, and TNFα; as well as the chemokines CXCL8/IL8, CCL2/MCP-1, and CCL3/MIP-1α; ;and other small molecule inflammatory mediators such as

nitric oxide, cyclooxygenase-2-derived lipids, 4-hydroxynonenal, nitrotyrosine, and high-mobility group protein B1 (HMGB1) (Cobelli et al. 2011; Steinbeck et al. 2014; Kzhyshkowska et al. 2015; Hallab and Jacobs 2017). In coordination, these numerous pathways further augment cellular infiltration and inflammation.

Uptake of particulate metal debris by macrophages through phagocytosis is a key mechanism by which implants may trigger inflammatory responses (Nich et al. 2013; Nich and Goodman 2014; Athanasou 2016). The specific mechanisms of uptake of metal debris by phagocytic cells is dependent on the size, shape, and chemical composition; by extension, these parameters impact downstream inflammatory and immunologic responses. Activation of the NALP3 complex is dependent upon the size, shape, and chemistry of metal debris (Caicedo et al. 2009; Cobelli et al. 2011; Scharf et al. 2014). Phagocytosed metal particles less than 10 µm in diameter are endocytosed and transported to lysosomes where the acidic microenvironment of these vesicles promotes particle corrosion, stimulating the further release of metal ion species (Hallab and Jacobs 2009; Gill et al. 2012). Because metal particles are resistant to complete degradation by lysosomes, cell death is a common endpoint for macrophages responding to metal debris, further perpetuating inflammatory signaling.

Particulates too large to be engulfed by an individual cell may trigger the fusion of macrophages, resulting in the formation of multinucleated, syncytiated foreign body giant cells (FBGCs) to sequester indigestible particles. This process, dubbed “frustrated phagocytosis”, has a central role in the formation of foreign body granulomas and perpetuation of implant-associated inflammatory responses (Klopfleisch and Jung 2017). Metal debris released from implants promotes the formation of FBGCs (Shahgaldi et al. 1995). Histological tissue sections from patients with failed implants, often evidence FBGC surrounding large metal debris, even in distal tissues. (Anderson, Rodriguez, and Chang 2008; Cobelli et al. 2011).

Neutrophils are also a canonical feature of the acute response to implanted devices and are implicated in adverse responses to metal implants and metal debris. Neutrophils rapidly mobilize to the site for 2-3 days following the implant; however, their lifespan *in situ* is short-lived. Production of IL-1α, IL-1β, and TGFβ by macrophages in response to metallic debris augments neutrophil recruitment (St Pierre et al. 2010; Akbar et al. 2012). This rapid response by neutrophils may be characterized as an acute highly localized stress program, through the release of proteases, lysozymes, and reactive radicals in the form of extracellular traps (NETs), contributing to opsonization, clearance, and scavenging at the implant site (Liu et al. 2014; Jhunjhunwala et al. 2015; Jorch and Kubes 2017). Several of these mechanisms implicate neutrophils in the initial production of metallic debris, via production of oxidizing agents and pro-inflammatory chemokines and cytokines (Sutherland et al. 1993; Labow, Meek, and Santerre 2001; Goncalves, Chiasson, and Girard 2010; Ye et al. 2010). Persistent accumulation of neutrophils following the foreign body reaction may be an indicator of maladaptive responses to a metal implant, potentially predicting adverse events, particularly septic modes of implant failure (Grammatopoulos et al. 2016).

Mast cells also participate in acute inflammatory responses to metal implants and possibly the immunopathology associated with device failure. Release of histamine by tissue-resident mast cells is a key instigator of the recruitment of phagocytic cells to the implant site, by driving expression of adhesion molecules on endothelial cells (Tang, Jennings, and Eaton 1998; Zdolsek, Eaton, and Tang 2007). Histologic signatures associated with dendritic cells and eosinophils can also be found in association with metal orthopedic devices (Thewes et al. 2001). While the roles of these cell types in biological responses to metals are less understood, the importance of dendritic cells in eliciting and

programming T cell responses implies a role for these cells in amnestic T cell-driven responses (Keselowsky and Lewis 2017).

6.3. Adaptive Immune Responses to Metal Implants

Evidence supports the involvement of adaptive, acquired immunity in normal biological responses to metal implants; however, research is more weighted towards roles for maladaptive acquired immune mechanisms in pathological responses to metal wear debris. Ectopic lymphoid structures are often found in association with failing implants (Willert et al. 2005; Mittal et al. 2013). Histological evidence demonstrates lymphocytes co-localizing with macrophages and giant cells in the fibrous tissues surrounding joint arthroplasties and other metal implants, particularly in the context of failing implants (Voggenreiter et al. 2003; Krenn et al. 2014; Perino et al. 2018). Furthermore, lymphocytes extracted from tissues surrounding implants are responsive to stimulation with metal ions (Hallab et al. 2008; Hasegawa, Iino, and Sudo 2016).

Together, these lines of evidence imply that metal implants may be capable of evoking a measure of immune "memory". The lymphocyte lineages, including T cells and B cells, contain the amnestic, "memory" features of lasting acquired immunity through selective programming and fating of specific lymphocyte clones. Moreover, these cell lineages are central in orchestrating the recruitment, activation, and effector functions of other cells of the immune system, in an ongoing process of dynamic response through cellular and molecular crosstalk. The predominance of lymphocytes in some forms of implant-associated ectopic lymphoid structures has led to the categorization of these adverse responses as *Aseptic Lymphocytic (Lymphocyte-dominated) Vasculitis-Associated Lesions (*ALVAL) (Davies et al. 2005; Willert et al. 2005; Campbell et al. 2010). Significant gaps remain in understanding the role of adaptive, acquired immunity in normal responses to implant, implant failure, and other adverse events. While metal allergies have been shown to be among the most common contact hypersensitivities (Zug et al. 2009), causative relationships between allergic reactions and adverse outcomes from metal implants remain contentious (Granchi et al. 2006; Thyssen et al. 2010; Granchi et al. 2012; Wawrzynski et al. 2017).

T cells require cognate interaction between their T cell receptor (TCR) and antigenic peptide embedded in major histocompatibility proteins (MHC) found on the surface of antigen-presenting cells. Metal ions have been proposed to act as haptens by forming coordinate intramolecular complexes with MHC proteins and antigenic peptides (Lu et al. 2003; Clayton et al. 2014a). Other reports suggest that metal ions can catalyze cross-linking of the TCR/MHC complex (Moulon, Vollmer, and Weltzien 1995; Gamerdinger et al. 2003; Catelas et al. 2015). T cells are consistently reported to appear in the tissues adjacent to implants in individuals with -well-functioning implants as well as proximal ectopic lymphoid structures (Willert et al. 2005; Mahendra et al. 2009; Kwon et al. 2010; Mittal et al. 2013). Although the presence of T cells near an implant is not inherently indicative of a maladaptive response, histological evidence suggests that number of cells present should be considered as T cells are much more numerous in tissues surrounding failed implants (Hasegawa, Iino, and Sudo 2016; Paukkeri, Korhonen, Hamalainen, et al. 2016). In contrast, circulating T cell numbers in peripheral blood do not appear to associated with implant-related ALTR (Hallab et al. 2008; Catelas et al. 2015), although these numbers are generally diminished following implant surgery (Granchi et al. 2003; Penny et al. 2013). The discrepancy of these findings suggest that pathologically maladaptive T cell responses may be of greater

importance at implant sites and in nearby tissues, than in circulation. Moreover, the presence of metal-responsive T cells may not necessarily be predictive, much less causative of adverse response. Functional specialization and effector programming of these cell types, associated with lineage differentiation, may be a more important outcome, as an indicator of coordinated responses (Budinger and Hertl 2000; Svedman et al. 2014).

Functional responses by $CD4^+$ T helper cells (Th) to metal implants depends on the metal composition of the implant, and often correlates with blood metal concentrations. $CD4^+$ T cells from circulation or harvested from tissues demonstrate signs of responsiveness to metallic antigens, including proliferation, expansion, and phenotypic markers associated with activation (Whittingham-Jones et al. 2008; Hallab et al. 2010a; Kwon et al. 2010; Dapunt et al. 2014; Hailer et al. 2014; Revell et al. 2016; Markel et al. 2018). The involvement of $CD4^+$ T cells in responses to metal implants implicates soluble cytokines produced by these cells as essential mediators of their contribution to overall coordination of immune responses to metal.

Cytokines associated with effector differentiation of $CD4^+$ T cells and their functional coordination of other immune effectors have been shown from patients with metal implants, including: Th1 (e.g., interferon-gamma [IFNγ] and tumor necrosis factor-alpha [TNFα]), Th2 (e.g., interleukin-4, -5, and -13 [IL-4, IL-5, IL-13]), Th17 (e.g. IL-17), Th9 (e.g. IL-9), and regulatory T cells (Tregs, e.g. IL-10, TGFβ) (Granchi et al. 2003; Schierano et al. 2003; Hallab et al. 2008; Summer et al. 2010; Hallab et al. 2013; Vermes et al. 2013; Liu et al. 2014; Perino et al. 2014; Catelas et al. 2015; Singh et al. 2015). Regulatory T cells (Tregs) have been implicated in wound healing through attenuation of inflammatory IFNγ signaling and macrophage recruitment (Nosbaum et al. 2016).Recent evidence implicates IL-17-producing Th17 cells in mediating local chronic inflammation in response to metallic implant (Samelko et al. 2019). These studies, taken collectively, are difficult to parse for conclusions of predominance and balance among these diverse cell subsets; and; and moreover, differences in pathologic outcomes and methodologies (Singh et al. 2015).

Animal modeling studies support a view in which instructive signals from innate immune and inflammatory recognition of metal implants, debris, or ions drive effector differentiation among $CD4^+$ T cells, which in turn feedback to innate and inflammatory effector mechanisms. By extension, this effector differentiation among $CD4^+$ T cells may represent a decisive checkpoint in determining persistent effector responses to metal implants, from NLRP3/IL1/IL17-axis inflammation or IL4-mediated allergic hypersensitivity to Treg-mediated tolerance (Roelofs-Haarhuis et al. 2003; Mishra et al. 2011; Ashrin et al. 2014; Du et al. 2018; Samelko et al. 2019).

It remains unclear to what extent the $CD8^+$ Cytotoxic T cell (CTL) compartment changes in response to metal implants. Several studies have reported conflicting numbers of $CD8^+$ CTLs present following implant procedures (Granchi et al. 1995; Granchi et al. 2003; Hart et al. 2009; Hailer et al. 2011; Hallab et al. 2013). IFNγ-producing $CD8^+$ CTLs can be found in the peripheral blood of implant recipients, but do not distinguish between pathological and normal, healthy responses to implant (Catelas et al. 2015). $CD8^+$ CTLs responsive to nickel haptens can be found in patients with nickel contact hypersensitivity, underscoring the role of this cell lineage in delayed-type (type IV) hypersensitivity responses (Traidl et al. 2000). $CD8^+$ CTLs can be found in association with periprosthetic tissue; however, it is unclear if cytotoxic effector functions of $CD8^+$ T cells, i.e., perforin and granzyme B production, participate in responses to metal implants (Perino et al. 2014).

Specific responses of B-lymphocyte (B cells) to metal implants and metal debris is unclear. B cell numbers appear to remain consistent in individuals with metal implants (Granchi et al. 2003; Hart et al. 2009). In pathological situations, such as metal hip implant failure, B cells are a consistent feature in the tissues adjacent to metal-on-metal total hip replacement (Davies et al. 2005; Mittal et al. 2013; Perino et al. 2014; Paukkeri, Korhonen, Hamalainen, et al. 2016). *In vitro*, B cells from patients with metal implants activate in response to stimulation with metals (Hallab et al. 2010b). Histological evidence also supports signs of B cell activation in tissues associated with failing metal implants, specifically the costimulatory molecules TNFSF13B/BAFF and TNFSF13/APRIL (Mittal et al. 2013).

The most significant role for B cell-mediated immunity in responses to metal may be through roles for B cell-produced antibodies to metal haptens in mediating immediate type I, II, and III hypersensitivity reactions, in contrast to T cell-centered dermal hypersensitization described in Section 7.2.3 (Singleton et al. 2016). Antibodies reactive to haptenized metal ions can be found in patients following stable implantation of cobalt-chromium implants (Yang and Merritt 1994). While IgM antibodies to metal haptens were most prevalent in this study, significant portions of the cohort also carried class-switched IgG, IgA, and IgE antibodies – suggesting that active B cell responses to metals are common, and not intrinsically associated with maladaptive pathology (Merritt and Rodrigo 1996).

6.4. Tissue and Organ Localization of Inflammatory Responses to Metal Implants

While many molecular, cellular, and signaling pathways associated with inflammatory and immune responses to metal implants are shared across device types, intended uses, anatomy, and physiology, there is a growing appreciation for device-tissue interface as an independent dimension of functional specialization in inflammatory and immune processes. At the intersection of anatomy and physiology, specific cellular subpopulations and specialized pathways are known to exist within many tissue types and solid organs. In this section, some of these specialized response pathways will be addressed. Similarly, other location- and tissue-specific context can inform and modulate common pathways through which metal devices and host response interact.

6.4.1. Orthopedic Devices

One significant failure mode for orthopedic implants is associated with periprosthetic osteolysis: bone loss which may lead to loosening of the device, causing pain and possibly failure. Resorption of bone is performed by osteoclasts, a multinucleated cell dependent on signaling through M-CSF and RANK-L for development from myeloid and embryonic precursors (Teitelbaum 2000; Epelman, Lavine, and Randolph 2014; Ono and Nakashima 2018). Osteoclasts express adhesion molecules and chemokine receptors that specify their localization to bone, cartilage and joint; specialized programs for calcium metabolism and acidification; as well as proteases including collagenases, proteases, cathepsins, and matrix metalloproteinases (MMPs) (Vaananen et al. 2000). The balance of osteoclastogenesis and osteogenesis by osteoblasts is thought to be a dynamic process, integrating a network of inflammatory, metabolic, and immune inputs for maintenance of skeletal integrity (Suda et al. 1999). Dysregulation of these signaling networks is central in osteoporosis and several congenital bone malformities (Cadosch, Gautschi, et al. 2009; Park-Min 2018).

As immediate regulators of bone metabolism and remodeling, osteoclasts have been well studied for their integration of local inflammatory signals and immediate responses to implanted metals

(Greenfield, Bi, and Miyauchi 1999). By proximity, osteoclasts are immediate sensors of metals used in orthopedic implants. Osteoclasts have been shown to be sensitive to phase transitions in nitinol as well as surface texture of titanium alloys (Muhonen et al. 2005; Matteson et al. 2016). Osteoclasts couple production of pro-inflammatory cytokines (e.g., IL1β, IL6, TNFα) and chemokines to corrosive oxidation and uptake of metal particulates (Cadosch, Chan, Gautschi, Simmen, et al. 2009; Cadosch, Al-Mushaiqri, et al. 2010; Cadosch, Gautschi, et al. 2010). A large study of orthopedic explants demonstrated clinical evidence of corrosion consistent with these cellular mechanisms (Di Laura et al. 2017).

The composition of metallic orthopedic implants has broadly advanced towards facilitating favorable host responses (Navarro et al. 2008). Extensive work has specifically focused on the ability of titanium ions and particles to enhance osteoclastogenesis – the differentiation of osteoclasts from monocytic precursors, and the acquisition of osteolytic effector functions in these cells (Brinkmann et al. 2012; Pasold et al. 2017; Lotz et al. 2018). Evidence from *in vitro* studies indicate that many metal ions can induce or enhance differentiation of osteoclasts from monocytic precursors (Cadosch, Chan, Gautschi, Meagher, et al. 2009; Konig et al. 2017). Osteoclastogenesis may not necessarily be a common response to all metal species, however (Rousselle et al. 2002). Metal ions derived from calcium phosphate bone cements demonstrated pleiotropic effects on differentiated osteoclasts, modulating their catabolic enzymatic activity and survival (Bernhardt et al. 2017). Metals less commonly found in orthopedic implants, including gold and zinc, may even suppress osteoclastogenesis through antioxidant mechanisms (Sul et al. 2010; Park et al. 2013). Additional preclinical investigation has sought to modulate or suppress the induction of osteoclastogenesis through pharmacologic or biomaterial additives (Lee et al. 2016; Hu et al. 2017; Zhu et al. 2017; Cordoba et al. 2018).

Nonclinical animal models have provided evidence that suppression of inflammatory cytokine signaling may have clinical utility in preventing or limiting maladaptive osteolytic responses to metal implants (Dong et al. 2008; Eger et al. 2018). Metal ions released by oxidative metal corrosion may not trigger osteolysis, but may instead serve as critical amplifiers of inflammatory pathways that contribute to osteoclastogenic development, programming of osteoclastic functions, and crosstalk with other immune and inflammatory mediators (Magone, Luckenbill, and Goswami 2015). Targeted inhibitors of osteoclastogenesis are under investigation for a variety of osteolytic disorders, including osteolysis associated with prosthetics (Looney et al. 2006).

6.4.2. Neurologic Devices

The central nervous system (CNS) is composed of diverse cell types including neurons, glia, pericytes, and endothelial cells, many of which are capable of inflammatory and immune functions in health and pathological conditions. The blood-brain barrier (BBB) represents a major boundary and regulator of the exchange of cells, proteins, and numerous metabolites: water, electrolytes, glucose, amino acids, and fatty acids. Tight junctions at the BBB interface are maintained by crosstalk between endothelia, pericytes, and astrocytes. The classical view of the CNS as a canonical site of “immunologic privilege” due to the BBB has been refined in recent years through the study of highly specialized lymphatics associated with the CNS (Aspelund et al. 2015; Louveau et al. 2015).

Metallic medical devices used in neurological applications include electrodes for deep brain stimulation, nitinol coils for neurovascular interventions, and nitinol blocks used in vertebral repair. Deep brain electrodes are used for therapeutic stimulation of neurological regions associated with Parkinson’s

disease, epilepsy, Tourette's syndrome, chronic pain, or compulsive disorders (Okun 2012; Fisher 2013; Boccard, Pereira, and Aziz 2015; Graat, Figee, and Denys 2017). An implanted pulse generator (IPG), placed in the chest or abdomen, produces electrical pulses intended to correct abnormal electrical signals or induce the release of neurotransmitters. Conductive leads run subcutaneously from the IPG to intracranial electrodes through a burr hole in the skull.

Implanted devices such as intra-cerebral electrodes may activate microglia, CNS-specialized resident macrophages, via TLR4 signaling (Hermann et al. 2018). Irrespective of signaling pathway, the insertion of intra-cerebral electrodes results in acute injury triggered by microglia and astrocyte activation, leading to tissue encapsulation of the electrode. The inflammatory response can impede electrical signals from the brain, complicating experimental evaluation (Kozai et al. 2012; Kozai et al. 2014).

Additionally, oxidative corrosion of nickel-containing stimulatory electrodes may liberate nickel ions in the CNS. Metals may be disruptive of multiple pathways in neural tissues: competing with ion channels, blocking electrolyte flux, inducing protein kinase C signaling, and causing proapoptotic arrest of the cell cycle in neurons (Karpen, Loney, and Baylor 1992; Slotkin and Seidler 2009, 2010). While many of these pathways are not restricted to neuronal tissues, surgical implantation may render this anatomical compartment uniquely accessible.

6.4.3. Cardiovascular Devices

Complications and adverse events associated with metallic cardiac and vascular implants often center on thrombus formation resulting from activation of coagulation cascades. Endothelium injury and foreign body placement lead to the activation of platelets at the site of the implant with recruitment of circulating leukocytes. Coagulation occurs through convergent extrinsic and intrinsic pathways, leading to generation of thrombin and fibrinogen, and conversion to fibrin (Smith, Travers, and Morrissey 2015). Extensive crosstalk between coagulation, complement, and inflammation inherently couple outcomes from these pathways (Mercer and Chambers 2013; Lupu et al. 2014; Conway 2018). The ultimate biocompatibility of a device will be influenced by both inflammation and coagulation.

Metallic stents are good examples of cardiac devices that can be used to elucidate the interactions of device characteristics or features with coagulation processes. These devices can be manufactured using a variety of designs, expansion mechanisms, and metallic compositions including stainless steel, nickel, titanium, chromium, and cobalt. Research studies have found that the adsorption of fibrinogen and platelet activation to nitinol surfaces is dependent on surface chemistry and topography; specifically, titanium content enhanced the adsorption of fibrinogen (Shabalovskaya et al. 2008; Canoa et al. 2015). In addition, nickel ions and particulates have been particularly well-studied for enhancement of platelet aggregation, through the induction of plasminogen activator inhibitor-1 (PAI1), and autoactivation of factor XII (Andrew, Klei, and Barchowsky 2001; Riondino et al. 2001; Mutch, Waters, and Morrissey 2012). Mechanistically guided strategies for coating devices with biomolecules, drugs, or polymers to strategically facilitate favorable responses are an active and continually developing area of investigation (Tepe et al. 2006; Nazneen et al. 2012).

6.4.4. Oral and Dental Implants

In the oral cavity, interactions between host response and metallic dental implants are highly influenced by the oral microbiota. The highly diverse communities of bacterial and fungal microbes within the oral habitat (Pokrowiecki et al. 2017); the composition of the microbiome in the oral habitat is among the most diverse in the human body (Human Microbiome Project 2012). There are many device characteristics that influence microbial colonization and composition. Roughness of metallic surfaces correlates with initial microbial colonization (Chin et al. 2007). Metallic composition of dental alloys is a significant modulator and determinant of bacterial colonization and outgrowth in a manner that can be selective for microbial species, influencing the composition of oral microbial communities (Nakajo et al. 2014; Svensson et al. 2014; Urushibara et al. 2014).

Oral microbiota largely survive within biofilms – polyglycan matrices, composed of both microbial and host proteins (Perrin et al. 2009), providing a dynamically regulated habitat for bacterial and fungal microbiota. Bacteria embedded in biofilms have been shown to communicate via small molecules, resulting in coordination of their outgrowth and adaptation via quorum sensing across species (Jayaraman and Wood 2008; Hojo et al. 2009; Huang, Li, and Gregory 2011; Willems, Xu, and Peters 2016). This community organization and response is thought to underlie the acquisition of pathogenicity and virulence factors, including antibiotic resistance (Shao and Demuth 2010).

The development of microbial biofilms associated with metallic dental and orthodontic devices can promote carious lesions and gingival disease (Eliades and Athanasiou 2002). Nickel surfaces have been shown to elicit biofilm formation by driving microbial expression of Curli, an extracellular amyloid fibrous protein (Perrin et al. 2009). Microbial biofilms elicit an acidic, oxidizing microenvironment in collaboration with host inflammatory processes, possibly leading to eventual peri-implantitis (Rodrigues et al. 2013). Bacterial lipopolysaccharide (LPS) was shown to further facilitate corrosion of titanium alloys, particularly in the weakly acidic oral environment (Yu et al. 2015). These electrochemical modes of corrosion may enhance or synergize with mechanical wear or tribocorrosion in facilitating failure of dental implants (Mathew et al. 2012).

Oral microbial composition and biofilms exert immunomodulatory pressures on host response. As with many other mucosal habitats, microbiota communities elicit low-grade, tonic inflammatory and immune signaling in normal healthy conditions (Belkaid and Hand 2014). Oral microbial communities effectively induce numerous pro-inflammatory cytokines and chemokines including IL1β, IL6, CXCL1, CXCL3, CXCL8/IL8, GM-CSF, and TNFα (Ramage et al. 2017). Pathogenic and opportunistic overgrowth and dysbiosis selectively retune these signals; periodontic microorganisms elicit host responses involving NALP3 inflammasome activation and subsequent expression of pro-inflammatory IL1β and IL18 as well as osteoclastogenic RANK-L (Bostanci et al. 2007; Bostanci et al. 2009; Hamedi et al. 2009). Recruitment of neutrophils to oral tissues is particularly key in amplifying homeostatic basal inflammatory signaling into persistent, pathogenic responses (Pokrowiecki et al. 2017). Biofilm microbial ecology and host responses to implant-associated microbes at other anatomic sites have been implicated in infectious and septic modes of implant failure (Costerton, Montanaro, and Arciola 2005; Arciola et al. 2015; Arciola, Campoccia, and Montanaro 2018).

6.4.5. Urogenital Devices

The female reproductive tract bears specialized subclasses of immunologic cell types: uterine natural killer cells (uNK), and several unique dendritic cell professional antigen-presenting cell subsets, in addition to canonical mainline leukocyte lineages (Manaster and Mandelboim 2008; Lee et al. 2015). The proportions and functions of these cells, as well as structural organization are dynamically regulated over the course of the normal menstrual cycle (Park and Yang 2011). In addition to regulating host interactions with the cervicovaginal microbiota, many of these cell types also participate in tissue remodeling through the menstrual cycle, as well as maternofetal tolerance (Juretic et al. 2004; Park and Yang 2011; Ruocco et al. 2014; Feyaerts et al. 2017).

Among the devices intended for use in the urogenital and reproductive tracts, implantable contraceptive devices, including intrauterine systems (IUS), are among the most common. Once implanted, copper-based IUSs (Cu-IUS) produce localized inflammation, which is characterized by recruitment of monocytes, neutrophils, lymphocytes, and plasma cells and sometimes may lead to inflammatory remodeling of the endometrium and associated tissues (Reinprayoon 1992; Wollen et al. 1994; Ortiz and Croxatto 2007). By design, the mechanisms of contraceptive action for these devices include release of cuprate ions, which in turn increase reactive oxygen and decrease reactive nitrogen in the uterine cavity (Ortiz, Croxatto, and Bardin 1996; Pradhan, Gupta, and Ganguli 1997; Anjalika et al. 1999). Cu-IUSs may be associated with systemic elevation of acute phase proteins, as well as local increases of IL1β, GM-CSF, TNFα, and soluble IL2 receptor (Shaarawy et al. 1981; Ammala et al. 1995; Shobokshi and Shaarawy 2002).

Causative mechanistic relationships between general IUS contraception and pelvic inflammatory disease are unclear (Ross 2013; Hubacher 2014). IUS can develop microbial biofilms following insertion (Pal et al. 2005). (Mohllajee, Curtis, and Peterson 2006; Sufrin et al. 2012; Curtis et al. 2016). Installation of copper or levonogestrel-eluting IUS is not associated with alterations of the vaginal microbiome ecology (Jacobson et al. 2014; Bassis et al. 2017). Furthermore, evidence does not support a causative relationship for bacterial vaginosis, associated with IUS (Meirik 2007). Together, these data support that microbial dysbiosis may not represent a necessary mechanistic link between IUS and PID.

Inflammation-related mechanisms are incorporated into the design of permanent hysteroscopic sterilization with the Essure titanium-nickel device; post-inflammatory fibrogenic occlusion of the fallopian tubes was mostly attributed to the non-metal device component – PET fibers (Dhruva, Ross, and Gariepy 2015). Evidence for a causative relationship between Essure and contact hypersensitivity to nickel is limited and ambiguous (Adelman, Dassel, and Sharp 2014; Teo Wendy and Schalock 2016; Camara et al. 2017; Siemons, Vleugels, and van Eijndhoven 2017); (Franchini et al. 2017), suggesting the involvement of diverse biological responses in Essure-related adverse outcomes.

6.5. Conclusions, Summary, Inflammatory Regulation Underlying Clinical Outcomes

Historically, as evidenced by the widespread use of the term “metal allergy”, deleterious responses were considered to only encompass adaptive immunity-predominated hypersensitivity. We now have more specific understanding of the overall role of inflammation and critical contribution of innate immune processes that determine eventual success or failure of an implanted device. This updated more holistic

view indicates that inflammatory responses elicited by implant presence and/or its debris employ both types of immunity (adaptive and innate) and decisive checkpoints for the eventual success or failure of metal-containing implant devices involve complex immunologic crosstalk that may propagate dysregulation of pro/anti-inflammatory balance and result in clinical manifestations, as discussed in the next section.

7 CLINICAL RESPONSE TO METAL IMPLANTS

The clinical response to metal implants is complicated and no simple explanation for the wide variety of reported adverse responses is available. Despite commonly used terms such as "metal allergy" or "metal hypersensitivity", current published evidence suggests that allergic mechanisms alone do not explain most responses to metal implants. Harmful responses, when they do occur, are likely the result of device, biomaterial, and patient-related factors. Individual patient susceptibility plays an important role in the outcome.

Recent issues with metal-on-metal orthopedic implants and gynecological metal implants highlighted concerns about the potential safety of certain types of metal implants. A broad spectrum of clinical responses have been reported and often more than one response can arise in the same patient. The entire spectrum of local and systemic findings related to metal implants is incorporated into the term "adverse reaction to metal debris" (ARMD). More frequent ARMDs include local responses such as pain, skin rash, tissue destruction including bone loss (osteolysis), escape of fluid from the joint (joint effusion), and solid and cystic masses called pseudotumors. Systemic responses such as depression, hearing loss, vertigo (dizziness), and neurologic and cardiac damage have also been reported by patients that have metal implants, although the determination of whether the metal caused the event(s) is often not possible.

Standard tests, such as metal ion levels in the blood stream or skin patch tests for metal allergies, correlate poorly with adverse responses. In some cases, patients with adverse diagnostic findings present no symptoms. For this reason, management of patients with metal implants is divided into proactive monitoring for asymptomatic patients and more aggressive diagnostic and therapeutic approaches for patients with clinical symptoms.

7.1 INTRODUCTION

While the possibility of adverse health outcomes in patients with metal implants was recognized decades ago, recent issues with metal-on-metal (MoM) orthopedic implants and gynecological fallopian metal implants has heightened concerns about the potential safety of metal implants in general. Although the accumulated evidence is not sufficient to fully explain the nature of adverse responses, a broad spectrum of clinically manifested responses (both local and systemic) has been reported in patients with various metal implants. The purpose of this section is to review clinically observed adverse responses, factors that may impact a patient's response to a metal implant, and limitations imposed by the current lack of consensus regarding terminology used to describe metal-implant related adverse outcomes. These contexts are highly diverse: patient history, genetic background, variations in environment and lifestyle, and underlying disease and comorbidity.

7.2 TERMINOLOGY PERTAINING TO POTENTIAL CLINICAL, IMAGING, AND MORPHOLOGICAL MANIFESTATIONS OF METAL IMPLANT-RELATED ADVERSE OUTCOMES

The Event Problem Code terminology developed by CDRH for use with medical device adverse event reporting, Patient Problem Code Hierarchy Subset: Patient Problem/Medical Problem[8] includes some terms pertaining to implant-related bioresponses. As an example, *Foreign Body Reaction* (FBR) (C50444; FDA 1868) is described as "a granulomatous inflammatory reaction evoked by the presence of an exogenous material in the tissues, a characteristic feature of which is the formation of foreign body giant cells". This FBR definition includes a subcategory of the Host Tissue Reaction (C50586; FDA 1297) defined as "growth of tissue in or around a foreign body as the body's antibody response to the foreign body". However, implant-elicited host responses are not limited to tissue growth and they are not necessarily caused by an antigen-antibody reaction. No additional terms describing implant-related bioresponses (*e.g.,* pseudotumor) are present in the Patient Problem Code or other FDA-linked terminology sources such as NCI Metathesaurus or Individual Case Safety Report (ICSR) at the time of preparation of this report.

According to ASTM F2978−13 standard "Guide to Optimize Scan Sequences for Clinical Diagnostic Evaluation of Metal-on-Metal Hip Arthroplasty Devices using Magnetic Resonance Imaging "for diagnostic evaluation of patients implanted with MoM devices, Adverse Local Tissue Reactions (ALTR) can manifest as synovitis, bursitis, osteolysis, and pseudotumors, and their histological features can include *Aseptic Lymphocytic (Lymphocyte-dominated) Vasculitis-Associated Lesions (ALVAL)* (ASTM 2013b). Although ASTM F2978-13 provides guidance for the assessment of implant-related tissue changes, it is focused on MRI features and it does not provide further terminological definitions or histopathological details about the various ALTRs. The main standard on device-related terminology, ASTM F2809-10 "Standard Terminology Relating to Medical and Surgical Materials and Devices" , identifies general terms such as *wound* or *ulcer,* but it does not refer to the aforementioned or other implant-specific adverse outcomes (ASTM 2010). ASTM F561-13 "Standard Practice for Retrieval and Analysis of Medical Devices, and Associated Tissues and Fluids", the main standard for retrieval analysis, includes recommendations for gathering and analyzing periprosthetic fluid/tissue specimens, but it does

[8] For more details on Patient Problem Code Hierarchy, see Event Problem Codes; accessed May 6, 2019.

not provide the standardized terminology with corresponding histopathologic description of different ALTRs (ASTM 2013a).

Published evidence shows that different ALTRs may indicate different complication rates and, therefore, unique follow-up needs (Ricciardi et al. 2016), thus underscoring the importance of adequate terminology and correct interpretation of peri-implant findings (Nawabi et al. 2014). The ALTR-related definitions reflect development of the insights into ALTR nature, starting with the landmark article by Willert (Willert and Semlitsch 1977) who first described the macrophage-mediated *foreign-body reaction* and who later reported the possibility of a "*lymphocyte-dominated immunological answer,*" i.e., LYDIA which, in essence, is synonymous to ALVAL (Willert et al. 2005).

While the term ALTR refers specifically to *local* periprosthetic tissue changes, the entire scope of responses elicited by metal-containing implants can be encompassed by the term *Adverse Reaction to Metal Debris (ARMD)*. As a result, ARMDs can incorporate both local and systemic responses including elevated blood/serum metal ion levels (Reito et al. 2016), metallosis (i.e., metal debris deposited in periprosthetic tissues) and various ALTRs (Langton, Joyce, et al. 2011) such as the aforementioned ALVAL (Natu et al. 2012; Bitar and Parvizi 2015), pseudotumors (i.e., cystic or solid masses with immune cell infiltration and metallic debris inclusions) (Lainiala et al. 2014), and osteolysis (Ricciardi et al. 2016) . The term *metallosis* is frequently used for designating metal debris deposits, but it may also incorporate the presence of resultant tissue reactions, thus overlapping with the term ALTR. Although the terms ARMD and ALTR are most frequently used in reference to MoM hip implants, both of them can be applied to responses pertaining to metal-on-polyethylene (MoP) devices (Kiran and Boscainos 2015; Plummer et al. 2016). Further, the term ALTR can be used in reference to adverse local tissue responses to ceramic-on-polyethylene orthopedic implants (Campbell et al. 2014) as well as other non-metal devices.

There is an ongoing debate over how best to define the term implant-related '*allergy*', mostly due to the unclear nature of implant-related *hypersensitivity* (or reactivity) and the lack of reliable diagnostic tests for many of the possible manifestations (Wawrzynski et al. 2017). The possibility of developing *hypersensitivity* to the constituent metals in various implants is well established (Teo Wendy and Schalock 2016). However, there is little, if any, reported clinical evidence for an implant failure due to a true allergy (i.e., allergen-antibody mediated reaction as the main cause). Moreover, type IV hypersensitivity, the assumed mechanism of metal reactivity (Morshedi and Kinney 2014),is unlikely to be the main cause for all possible manifestations of ARMD, as indicated, for instance, by diagnostic insufficiency of T-cell-based tests for pseudotumors (Kwon et al. 2010). Maintaining that metal allergy remains a rare diagnosis of exclusion in cases with periprosthetic tissue reactions and that development of pseudotumors is likely driven by inflammatory responses to excessive wear debris rather than by metal allergy, Gross and Liu (2013, 2014) suggested the term *adverse wear (related) failures* (Gross and Liu 2013, 2014).

The terms *ALTR* and *ALVAL* are often used interchangeably, representing the terminological inconsistency that limits the entire scope of potential ALTRs to ALVAL (which is only one of its subtypes) and thus overemphasizes the role of ALVAL's lymphocyte-mediated tissue responses. Further, the terms *metal hypersensitivity (or sensitivity)* and *metal allergy* are also being used erroneously as synonyms (S. and A. 2016), despite the fact that the term sensitivity, unlike allergy, does not necessarily imply an allergen-antibody reaction. Clarifying the meaning of terms *sensitivity* and *toxicity* in relation to the

implant wear, host-related factors and inter-individual variability of responses, Gill et al. (2012) defined implant-related *toxicity* as an expected response to the excessive wear, and implant-related *sensitivity* – as an exaggerated response to the expected amount of wear.

7.2.1 Systemic ARMDs

Possible – local and systemic – ARMDs can be predetermined by the device-tissue interface. Orthopedic implants, for instance, are more frequently associated with pseudotumors and osteolysis, while metal sensitivity due to endovascular devices may contribute to adverse outcomes such as ISR, thrombosis, and Kounis syndrome (Koniari, Kounis, and Hahalis 2016). The latter self-named syndrome is characterized as acute coronary events associated with anaphylactoid, allergic, or other hypersensitivity insults (Kounis et al. 2014)

The likelihood of certain ARMDs may be also affected by implant-related constituent metals (*e.g*., Co/Cr *vs.* Ni or Ti) as well as predominant wear debris type (*e.g*., particles *vs*. ions). Implant-related metallic debris may cause systemic effects, mostly due to blood and lymphatic dissemination. In the highly-cited meta-analysis by Hallab et al. (2009), prevalence of metal sensitivity in patients with failed/failing implants was estimated to be 2-3 times that of all examined patients with metal implants (Hallab and Jacobs 2009). However, the reports of verifiable hypersensitivity remain relatively uncommon (Teo Wendy and Schalock 2016) and the mechanistic details of metal reactivity and corresponding clinical manifestations remain to be elucidated (Hallab and Jacobs 2009). Notwithstanding the limitations of current knowledge about ARMDs, the insufficiency of adaptive immune responses for explaining the entire ARMD spectrum is further evidenced by ARMD manifestations that affect different organs and imply varying pathogenetic effects, as discussed below.

7.2.2 Elevated Metal Ion Levels

While overt implant-related metal toxicity is rare, elevated serum/blood metal levels represent one of the most frequently reported adverse reactions with potential systemic effects. Even well-performing MoM arthroplasties can result in elevated blood/serum Co and Cr levels (Bitar and Parvizi 2015; Cheung et al. 2016). A systematic review of 11 randomized controlled trials (RCTs) and 93 epidemiological studies on metal ion levels (Co, Cr, Ti, Ni, Mo) in 9,957 patients with metal-containing hip implants identified elevated metal ion levels (whole blood, serum, plasma, erythrocytes, urine) in patients with MoM hip bearings (Hartmann et al. 2013). A summary of the six reviewed studies that reported metal ion concentrations with regard to MoM implant performance showed that cases with malfunctioning implants with ALTRs had higher Co levels compared to those with well-functioning implants. Differences in total body bone mineral density and bone turnover as well as some cardiac functions were found in patients with well-functioning MoM hip resurfacing *vs*. conventional hip replacements, suggesting that chronic exposure even to relatively low elevated metal ions may have systemic effects (Prentice et al. 2013). On the other hand, ALTR may develop in MoM hip patients without elevated serum metal ion levels (Tetreault M. 2018).

Systemic effects in response to metal orthopedic implants are frequently ascribed to Co and are referred to as cobaltism (Gessner et al. 2015; Cheung et al. 2016; Zywiel et al. 2016). According to the European multidisciplinary consensus statement, while Co values <2 µg/L are probably devoid of clinical concern, the range of 2-7 µg/L represents the threshold value for clinical concerns in unilateral MoM hip replacements (Hannemann et al. 2013). The excessive Co debris has been linked to trunnionosis, i.e., the phenomenon whereby wear particles are produced due to corrosion at the head-neck junction

(trunnion) in modular hip replacements (Fehring and Fehring 2015; Weiser and Lavernia 2017). However, potential systemic toxicity due to high Co levels is not limited to trunnionosis or MoM prostheses in general (Bradberry, Wilkinson, and Ferner 2014).

Conflicting evidence has been presented with regard to diagnostic and prognostic values of metal ion levels for identifying high-risk patients (Jacobs et al. 2004; Griffin et al. 2012; Hannemann et al. 2013; Cheung et al. 2016; Iqbal et al. 2017). In a recent meta-analysis, metal ion levels were deemed not useful as a screening test for ARMDs, mostly due to a large burden of false-positive results (Pahuta et al. 2016). As suggested even in the reports on possible correlations with ALTR (Campbell et al. 2014), elevated metal ion levels should not be used in isolation for clinical decision-making. As an example of relationships between metal levels and clinicopathological characteristics, in the study on MoM hips which identified two main pseudotumor phenotypes, i.e., macrophage- and T-lymphocyte-dominated,, both Cr and Co blood levels were significantly higher in cases with the macrophage-dominated responses (Paukkeri, Korhonen, Hämäläinen, et al. 2016). Interestingly, an inverse correlation was shown for the periprosthetic *tissue* metal content in relation to the immune response type: in failed small-diameter MoM hips, tissues with a predominantly lymphocytic response had much higher mean metal content than those with a macrophage-dominated response (Lohmann et al. 2013).

7.2.3 Different Manifestations of Systemic Hypersensitivity and Inflammation

Allergic dermatitis is one of the most recognized systemic manifestations of implant reactivity. With clinical features depending on its duration (Thyssen and Menne 2010), acute dermatitis is characterized by erythema, edema, papules, vesicles, and weeping, whereas chronic dermatitis tends to be scaly, dry, and fissured. In addition to *local* dermatitis, metal reactivity may result in *systemic* dermatitis with an extended range of cutaneous lesions (*e.g.*, eczema, scaling, pruritus, urticarial, and other rashes) as well as non-cutaneous reactions (*e.g.*, generalized pain, fever, syncope, palpitations, arrhythmia, serosal effusion, vasculitis, hair loss, poor wound healing, etc.) (Verma and Tobis 2011; Zurawin and Zurawin 2011; Morshedi and Kinney 2014; Wawrzynski et al. 2017).

Regardless of the device area, the relationship between metal ""allergy" and implant failure is considered controversial (Wawrzynski et al. 2017) and it remains uncertain whether true metal allergy causes device failure or developing device failure causes what may be considered metal ""allergy" (Thyssen and Menne 2010). Although the first report of cutaneous sensitivity (which was characterized as a foreign body response) to a metallic orthopedic implant was reported in 1966 (Foussereau and Laugier 1966), metal hypersensitivity and its sequelae, including allergic dermatitis, are the subject of ongoing debate, especially with regard to orthopedic devices. In a large-scale Danish linkage study (Munch et al. 2015), pre-operative metal allergy and positivity of patch test-based reactions to common metals were not directly associated with total knee arthroplasty related revision and other complications. As frequently cited evidence on the role of orthopedic implant-related allergy, the meta-analysis by Granchi et al. (2012) showed that the probability of metal allergy in patients with joint replacements was higher post-operatively and was further increased in cases with failed *vs.* stable implants; however, the predictive value of hypersensitivity testing was not conclusively demonstrated (Granchi et al. 2012).

Considering the concept of 'allergy' unproven in the orthopedics field, some authors described *sensitive* or *allergic* patients as the exception rather than the rule (Langton, Joyce, et al. 2011), further commenting that patients with hip implants are sometimes labelled "allergic" when little or no metal debris is found and when a heavy lymphocytic infiltrate is present. Some of these cases, however, may

lack comprehensive assessment of the wear and wear-related tissue changes that could have suggested an alternative etiology (Langton, Joyce, et al. 2011). Nevertheless, some reports presented typical cases of systemic dermatitis in patients with MoM hips, where metal sensitivity was confirmed by patch testing and the device relatedness of dermatitis was indicated by symptom resolution after device removal (Wong and Nixon 2014; Bizzotto et al. 2015). In a rare case report, a woman with total knee arthroplasty developed metal sensitivity which manifested as systemic dermatitis and severe hair loss which resolved after revision (Post, Orozco, and Ong 2013). Eftekhary et al. in a recent review summarized the current understanding of metal hypersensitivity in total joint arthroplasty (Eftekhary et al. 2018). These authors stated that "Currently, there are no guidelines for addressing suspected or known metal allergy preoperatively and there is no evidence-based support for either preoperative testing or routine use of hypoallergenic implants."

Most recently, concerns over implant-related systemic cutaneous lesions such as Systemic Contact Dermatitis (SCD) and Systemic Nickel Allergy Syndrome (SNAS) (Pizzutelli 2011; Bergman, Goldenberg, and Jacob 2016) were raised with regard to Essure, the permanent birth control device placed into the fallopian tubes.[9] However, SCD and SNAS may result from allergen exposure elicited via various routes (Goldenberg and Jacob 2015) and therefore may be potentially associated with various devices.

Autoimmune/Autoinflammatory Syndrome Induced by Adjuvants (ASIA) is another potential systemic response which has been reported to be associated with various, including metal, implants (Stejskal, Ockert, and Bjorklund 2013; Goren, Segal, and Shoenfeld 2015; Colaris et al. 2017). In the case series on 5 patients with different implants (including dental restorations) who were diagnosed with fibromyalgia, chronic fatigue syndrome, and other forms of systemic inflammation, the ASIA-like symptoms were thought to be triggered by metal implant-induced sensitization, as suggested by patch/LTT testing (Stejskal, Ockert, and Bjorklund 2013). As another example of possible metal-related systemic reaction, a 23-year-old woman who had a Ni-Ti chin implant for cosmetic reasons was diagnosed with ASIA, which manifested as high fever, fatigue, enlargement of the spleen and lymph nodes, musculoskeletal and abdominal pain and was accompanied by elevated ESR, anemia, and changes in urine, thrombocytes, and ferritin (Loyo et al. 2013). The patient's symptoms persisted during anti-inflammatory treatment including steroids but resolved after removal of the Ni-Ti implant.

Non-specific systemic symptoms such as fatigue and diffuse joint and body aches may be reported by patients with various implants. In some cases, these symptoms may resemble those of connective tissue diseases. However, no published evidence on the presence of serological testing profiles (e.g., anti-double stranded DNA; anti-nuclear antibodies) or other diagnostic criteria confirming the autoimmune nature of these symptoms and their causal relationship to the implant was found during the preparation of this paper. Although, the commonality between some implant attributed symptoms and those in known connective tissue diseases suggests that these conditions may share common inflammatory/immunological pathways which however may not be limited to allergy and autoimmunity.

Implant-related metals have been also implicated in systemic toxicity which may involve additional – other than hypersensitivity – mechanisms. Due to therapeutic use in anemia, Co is well known for its side effects, mostly hematological or neurological (Cheung et al. 2016; Zywiel et al. 2016). There is at least one reported case of fatal multi-organ failure with polycythemia and hepatotoxicity due to

[9] More details can be found in Section 7.5.6

extremely high serum Co levels (>6,000 µg/L) after Co-Cr hip arthroplasty (Cheung et al. 2016). There were at least 18 published cases (Zywiel et al. 2016) of systemic Co toxicity attributed to Co-Cr hip arthroplasty; a great majority of these cases reported more pronounced systemic toxicity at serum Co levels exceeding 100 µg/L; however, multisystem involvement was found in all examined cases, with neurological, cardiac, and thyroid effects seen more commonly.

7.3 Sex-Related Issues in Clinical Responses to Metal Implants

Sex-related differences can be found in many areas of biomedical research and clinical medicine. It is difficult to identify the complex mix of factors leading to these sex differences (Wizemann and Pardue 2001). Females also have higher rates of developmental dysplasia, rheumatoid arthritis, and osteoarthritis than their male counterparts (Caicedo et al. 2017). A significantly increased rate of failure among women undergoing MoM total hip arthroplasty (THA) was identified in the National Joint Registry for England and Wales (Latteier et al. 2011; Haughom et al. 2015). This observed sex difference was independent of femoral head size. There is evidence that sex differences in immune responses are responsible for the increased rate of failure in MoM hips (Caicedo et al. 2017) which is consistent with previous studies demonstrating a significantly higher rate of self-reported cutaneous metal sensitivity among females (Bloemke and Clarke 2015). In one study, 97.8% of arthroplasty patients self-reporting metal allergy were female (Nam et al. 2016). In a recent study, Caicedo et al. (2017) reported that using the lymphocyte stimulation index (SI), 49% of females had an SI ≥4 (reactive) compared with 38% of males, and implant-related level of pain was also significantly higher among females compared with males ($p < 0.0001$). These authors suggest that "In addition to anatomical and biomechanical sex differences, there may be inherent immunological disparities that predispose females to more aggressive adaptive immune reactivity to implant debris, i.e., metal sensitivity" (Caicedo et al. 2017).

7.4 Clinical Observations and Investigations of Systemic Responses to Metal Implants

7.4.1 Cardiotoxicity

There are a number of case reports describing Co-induced cardiotoxicity (Cheung et al. 2016) with possible permanent myocardial damage (Mosier et al. 2016) after implantation of a metal implant. A fatal Co-induced cardiomyopathy was recently described in a female patient with fractured ceramic hip implant who was revised to a MoP articulation and ten months post-revision, developed hip pain, dyspnea (difficulty breathing), worsening hearing loss, metallic dysgeusia (sense of taste), and weight loss (Fox et al. 2016). The causative role of Co toxicity in this case was evidenced from the increased Co levels in whole blood and urine, as well as the autopsy-based Co levels in the heart tissue and periprosthetic effusion (Fox et al. 2016). A recent Australian cohort study found that men with MoM (ASR XL) hip prostheses had a higher rate of hospitalization for heart failure compared to men with MoP hip prostheses (HR = 3.2; 95% CI: 1.6-6.5) (Gillam et al. 2017). Similarly, metallic head THAs, especially MoM hips in women and older patients, were associated with the slightly increased risks for dilated cardiomyopathy and heart failure in a cohort study based on the French national health insurance databases (Lassalle et al. 2018). Berber et al. evaluated 90 patients with either ceramic on ceramic, MOM hips with low ion levels, and MOM hips with high ion levels (>7ppm). In this study, there was no difference in cardiac MRI results. There was no difference in ejection fraction between any of the three

groups. The authors concluded that their study "excludes any clinically important association" between moderate metal ion levels and cardiotoxicity (Berber, Pearse, and Tennent 2013).

7.4.2 Neurotoxicity

Co neurotoxicity was described in a limited number of patients with malfunctioning hip replacements who displayed ocular, audio-vestibular, and cognitive symptoms over a range of Co ion levels (Tower 2010; Cheung et al. 2016). A Medicare-based query showed no significant difference in 5-year post-operative prevalence of pre-selected neurological diagnoses in cohorts with MoM and MoP replacements; however, both cohorts with metal-containing implants showed post-implantation increases in new diagnoses of peripheral neuropathy, sensorineural hearing loss, visual impairment, paresthesia (abnormal skin sensation), tinnitus (ringing in the ears), and vertigo (Bala et al. 2016). In a study on patients with neurological symptoms supposedly attributed to MoM or other implants (Leikin et al. 2013), the most frequent symptoms included fatigue, muscle aches, and tinnitus/hearing loss; among three reported cases of provisional demyelinating neuropathy, one case markedly improved after revision.

7.4.3 Thyroid toxicity

Although most of the published evidence on Co thyroid toxicity has been associated with causes not related to implants (*e.g.*, treatment of anemia), some reports mentioned hypothyroidism as a potential result of high serum/plasma Co levels (> 250 µg/L) following hip replacement (Cheung et al. 2016).

7.4.4 Cancer

Cancer concerns regarding metal implants are raised mostly due to *in vitro* carcinogenic effects exerted by metals such as Co and Ni as well as possible neoplastic changes in peri-implant tissues (Bitar and Parvizi 2015; Cheung et al. 2016; Zywiel et al. 2016).

A review of early epidemiologic studies on implant-related hematopoietic cancers found conflicting evidence, with only two studies suggesting an increased risk of lymphoma and leukemia after THA (Gillespie et al. 1996). The reintroduction of MoM hip implants heightened concerns about possible carcinogenicity of metal wear debris (Jacobs et al. 2003; Wagner et al. 2012), resulting in further epidemiologic studies.

A 30-year follow-up based on the Swedish Knee Arthroplasty registry showed a significantly higher overall risk of cancer among the osteoarthritis (OA) and rheumatoid arthritis (RA) patients with arthroplasty; however, only the risks of myelodysplastic syndromes and, to a lesser degree, prostate cancer and melanoma were associated with orthopedic implant-related metal exposure (Wagner et al. 2011). A population-based US study, which involved 1,435,356 person-years of follow-up and 20,045 cases of cancer, did not reveal an increase of overall risk of cancer following THA; however, the risks of prostate cancer and especially melanoma appeared slightly higher (incidence ratios: 1.12; 95% CI, 1.08-1.16 and 1.43; 95% CI, 1.13-1.79, respectively) (Onega, Baron, and MacKenzie 2006). The elevated melanoma risk was postulated to be from a long-term exposure to metal ions, particularly to hexavalent Cr which has been shown to have effects on melanocytes (Meyskens and Yang 2011).

In a linkage study based on the National Joint Registry of England and Wales (NJR), overall cancer risk was similar in patients with MoM hip replacements and other implants (Lalmohamed et al. 2013). A population based prospective longitudinal cohort study using the same registry also noted no increase in cancer risk with MoM bearing arthroplasty (Hunt et al. 2018). Similarly, no increased risk for any cancer

was found in the NJR-based linkage study on patients with hip replacements using MoM *vs.* alternative bearings (Smith et al. 2012). A Finnish study on patients with MoM (McKee-Farrar) *vs.* MoP hip replacements (Visuri et al. 2010) showed that after 20 years post-implantation, both cohorts had increased mortality compared to the general population; the MoM cohort had higher cancer mortality compared to MoP during the first 20 years post-implantation, but not thereafter. Another study using the Finnish registry also showed no increase in overall risk of cancer in their MoM cohort (Ekman et al. 2018).

In a large-scale Finnish cohort study on patients with MoM *vs.* conventional hip replacement, overall risk of cancer was not increased and overall risk of death was even lower, but the risks of soft-tissue sarcoma and basalioma were higher in the MoM cohort (Mäkelä et al. 2014). In a large-scale Scottish study on total hip replacement or resurfacing (Note: the study was not able to distinguish between MoM and non-MoM replacements), the risks for all cancers, prostate cancer, and especially multiple myeloma were slightly increased (Brewster et al. 2013).

Possible links between implant reactivity and certain cancers were also discussed in some case reports. Demehri et al. (2014) presented a rare case of aggressive cancer that, in the authors' opinion, was prompted by the metal implant-related chronic allergic contact dermatitis (ACD) located in the sun-exposed area (Demehri et al. 2014). A 46-year-old female with no prior history of skin cancer had an ankle fracture that was repaired using a Ni-containing metal rod for stabilization. After developing a non-healing skin lesion and testing positive for Ni allergy, she had the rod removed, but the skin lesions including significant erythema, oozing, and pain persisted. Three years later, she was diagnosed with Marjolin's ulcer, an invasive squamous cell carcinoma that developed in the ACD area over the implant site. In addition to this case of squamous cell carcinoma associated with orthopedic implant (Demehri et al. 2014), there were case reports linking squamous cell carcinoma to metal allergy due to dental restorations (Hougeir et al. 2006; Weber et al. 2012) as well as implant-related inflammatory responses in general (Jané-Salas et al. 2011).

Considering the recent evidence on breast implant-associated anaplastic large cell lymphoma (ALCL), some reports suggested possible development of ALCL in relation to other, including metal, implants. Palraj et al. (2010) reported the case of ALCL that was associated with a stainless-steel fixation plate implanted several years earlier for repair of a tibial fracture (Palraj et al. 2010). (Yoon, Choe, and Jeon 2015) described the case of mucosal CD30+ T-cell lymphoproliferative disorder that developed several years after placement of dental implants. Antigenic stimulation and chronic inflammation brought about by the presence of implants made of silicone, metal, or other (e.g., polyethylene terephthalate) materials have been suggested as possible neoplastic triggers (Palraj et al. 2010; Menter et al. 2019). Resembling lymphomas associated with other inflammatory conditions, implant-associated lymphomas are believed to share the following features: (1) development in the setting of prolonged inflammation, (2) localization to a confined body space (e.g., between an implant and the surrounding tissue), (3) a long latency period between the onset of the inflammatory process and the development of the lymphoid malignancy, and (4) the large-cell phenotype (Palraj et al. 2010).

In summary, while isolated reports exist of cancers associated with metal implants, data from multiple large registries has failed to support any increased risk of malignancy with metal implants.

7.5 Specific Device Areas

7.5.1 Orthopedic devices

While biologic responses to metals in orthopedics was discussed prior to MoM hip implants, the issue was brought to the forefront with the more widespread use of MoM hips (Merritt and Brown 1981).

MoM hip implants were first introduced in 1966 with the McKee-Farrar THR prosthesis (McKee and Watson-Farrar 1966). These implants were felt to have two potential advantages over conventional MoP THA. First, MoM articulations produced significantly less volumetric wear, and so were anticipated to reduce failure rates secondary to wear-induced degeneration of bone tissue (MacDonald et al. 2003). Second, metal acetabular components can be made thinner, allowing for large diameter femoral heads (Bolognesi and Ledford 2015) in both total hip replacements (THR) and surface replacement constructs. More than 1 million MoM articulations have been implanted since 1996 (Bolognesi and Ledford 2015). While most widely reported with regard to MoM hips, metal wear debris-related adverse reactions have also been associated with knee replacement (Gao et al. 2011; Lachiewicz, Watters, and Jacobs 2016; Klasan et al. 2019), spinal disc replacement (Guyer et al. 2011; Pettine and Hersh 2011; Berg S 2014), shoulder replacement (Khan et al. 2008; Berber, Pearse, and Tennent 2013; Morwood and Garrigues 2015; Kennon et al. 2019), shoulder suture anchors (Bauer and Harper 2017), intramedullary humeral nailing (Bauer and Harper 2017), and internal fixation screws (Barranco and Soloman 1972).

Concerns emerged when registries showed a significant, two-to three-fold increase in revision rates with MoM hips as compared to standard MoP hips (Bozic and al. 2012 {Bozic, 2012 #459 {Bozic, 2012 #459)). The reasons for failure were complex and defied easy explanation. It should be noted that while increased revision rates have been well documented for MoM THR, MoM resurfacing arthroplasty has not consistently shown these high rates of revision, with a 96.8% 10-year survival rate for one MoM resurfacing device when females and larger femoral heads were excluded (Ford et al. 2018). While MoM THR remains problematic, these and other authors have felt that MoM hip resurfacing may still show advantage for some subsets of patients (Quesada, Marker, and Mont 2008).

Metal ions can be generated not only at the junction between the femoral head and socket, but also at the junction of the head and stem of the femoral component (Langton, Joyce, et al. 2011), and in MoP THRs, at the junctions between modular components (Bernstein et al. 2016; Jennings, Dennis, and Yang 2016). This has been described as “trunnionosis” (Mistry et al. 2016). Metal ion generation has also been of concern with dual mobility hips (Markel et al. 2019). Multiple modular connections within a single hip system can further exacerbate this issue (Di Laura et al. 2018). The rate of revision for metal issues in MoP hips has been reported to be as high as 0.5% in a series of 2102 primary MoM THR (Persson et al. 2018) and trunnionosis revisions show a higher than expected complication rate (Dearborn 2019).

The release of metal particles and ions around the prosthesis can result in tissue changes such as necrosis, sterile hip effusions, and solid and cystic masses, termed pseudotumors (Bolognesi and Ledford 2015). The term “pseudotumor”, in reference to MoM orthopedic implants, was first used by Pandit et al. who described it as neither infective nor neoplastic soft tissue masses present in patients with hip resurfacing (Pandit et al. 2008). As suggested by the evidence of asymptomatic pseudotumors in patients with well-functioning prostheses (Williams et al. 2011; Hart et al. 2012), the true incidence of these tissue changes could be higher than estimated by incidental findings. Further confusing this issue is the documentation of regression and spontaneous remission of pseudotumors with time (Almousa et

al. 2013). Pseudotumors have been reported in as many as 32% of asymptomatic MoM hips, 25% of MoM resurfacing hips, and in 4% of asymptomatic MoP hips (Williams et al. 2011). A study by Saku et al. could not demonstrate a correlation between symptomatic pseudotumors and neurovascular compression (Saku et al. 2019). The associated soft tissue destruction created by pseudotumors can be significant (Eltit et al. 2017) and can lead to a substantial increase in complications with increased rates of instability and revision (Iqbal et al. 2017). In a study investigating correlations between wear and histological features in failed MoM hip resurfacings (Grammatopoulos et al. 2013), an exacerbated adaptive immune response was associated with only a small fraction of pseudotumors, whereas the heavy macrophage infiltrate with corresponding substantial necrosis was noted in all pseudotumors. Lymphocyte reactivity to Co, Cr, and Ni did not significantly differ in MoM hip resurfacing cases with pseudotumors compared to those without pseudotumors, further suggesting that type IV hypersensitivity can be hardly considered the dominant immune response driving development of pseudotumors (Kwon et al. 2010). Pseudotumors around implants have also been reported with ceramic-on-ceramic hips (Campbell et al. 2017), ceramic-on-polyethylene hips (Taheriazam and Saeidinia 2016) as well as modular total knee replacement (Christiner et al. 2018; Garbuz et al. 2019).

While pseudotumor represents the most profound soft tissue changes, osteolysis (i.e., bone loss) followed by aseptic loosening or fracture is the main adverse outcome affecting periprosthetic *bone* tissue. Similar to the role of innate responses in development of pseudotumors, macrophage-mediated cell death and inflammatory responses are emphasized in development of implant-induced osteolysis (Hallab 2016). While the adaptive responses with lymphocyte activation (frequently described as ALVAL) may accelerate a hypersensitivity-related failure of MoM hip devices, development of slower but more frequent osteolysis-related failure (aseptic loosening) most often occurs due to innate macrophage mediated-responses. According to the recently developed concept on the relationships between wear and cellular reactions representing two types of immunity (Campbell et al. 2010; Natu et al. 2012; Grammatopoulos et al. 2013; Chalmers et al. 2016), revisions with low wear tend to show higher ALVAL scores suggestive of lymphocyte-mediated hypersensitivity, while revisions with high wear tend to have lower ALVAL scores, but more profound macrophage-dominated responses. This concept, however, was not supported by all available studies (Chalmers et al. 2016).

The rate of metal reactivity related adverse outcomes, including early device failure requiring revision, are not similar across all types of MoM prostheses (Langton, Jameson, et al. 2011; Lainiala, Reito, and Eskelinen 2019), and can vary based on the prosthesis brand and the sizing of the implant, especially the femoral head (Bolognesi and Ledford 2015). At one extreme is a 40% 10-year revision rate for one MoM hip arthroplasty device type (Reito, lainiala, and Eskelinen 2019). There is also a substantial effect from component positioning (Mann et al. 2017), presumably due to increased wear from unevenly loading the ball and socket (termed edge loading) (Mann et al. 2017), as well as from multiple patient-related factors such as age, sex, and level of physical activity. These issues were well summarized in a commentary by Ayers (Ayers 2018).

Although some adverse outcomes (*e.g.*, allergic dermatitis, or ALVAL) in patients with orthopedic metal implants may include delayed hypersensitivity reaction (type IV) (Willert et al. 2005), many authors hypothesize that true metal allergy has little to do with the overall ARMD (Sidaginamale et al. 2013), or the failure of orthopedic implants in general (Thyssen et al. 2009; Thienpont and Berger 2013; Kim et al. 2015; Wyles et al. 2015; Bravo et al. 2016; Hjorth et al. 2016; Schalock et al. 2016; Teo Wendy and

Schalock 2016). However, other authors have found that orthopedic patients with numerous allergies of any type are at increased risk of revision (Nam et al. 2016; Otero et al. 2016).

In addition to the most frequently reported event, that of elevation of Cr and Co blood/serum levels, reported ARMDs in patients with metal orthopedic implants include rare cases of systemic toxicity, including dermatitis and hair loss (Post, Orozco, and Ong 2013), cardiac damage (Tower 2010; Gillam et al. 2017), and neurologic damage (Tower 2010). Systemic ARMDs have generally been associated with extremely high metal ion levels and have not always been reversible (Tower 2010). Neuropsychiatric symptoms in patients with MoM devices have also been reported (Green, Griffiths, and Almond 2017) as part of possible systemic responses to the elevated metal ion levels. However, neuropsychiatric evaluation is complicated by the expected differences in patient reactions to the possibility of an inferior outcome and multiple revision surgeries (Green, Griffiths, and Almond 2017). Neurocognitive reactions to MoM articulations may result in symptom magnification and thus, may further complicate the evaluation of cause and effect responses, including an elusive correlation between multiple allergies and arthroplasty outcomes (Nam et al. 2016; Otero et al. 2016).

Suggested treatment protocols for appropriate management of MoM hips vary but have traditionally been divided into options for symptomatic and asymptomatic patients (Bolognesi and Ledford 2015). Given the poor correlations between metal ion levels and radiographic (Matharu et al. 2017) or clinical symptoms, many recommend that asymptomatic patients can be followed with annual exams that do not necessarily involve metal ion evaluation (Bolognesi and Ledford 2015). Patients with pain and other symptoms may require a different course of action. Other causes of pain unrelated to the metal implant, especially infection, should be ruled out based on careful history taking, physical examination, and appropriate laboratory studies to rule out infection. Some recommend that patients should be particularly questioned about history of metal allergy/hypersensitivity. Following the history and physical examination, review of both the initial and serial postoperative radiographs should be assessed for loosening, osteolysis, and component position (Bolognesi and Ledford 2015). Symptomatic patients should have metal ion levels evaluated and have either ultrasound or special MRI techniques for use around metal implants such as metal artifact reduction sequence (MARS) MRI scans performed (Bolognesi and Ledford 2015), taking into account that elevated metal ion levels do not necessarily correlate with development of ARMD (Hjorth et al. 2016) and that some cases with advanced ARMDs are accompanied by normal radiographs and minimal symptoms (Matharu et al. 2017).

Many recommend that basic laboratory work using Complete Blood Count (CBC), sedimentation rate, C-reactive protein, and joint aspiration should all be considered. As illustrated in Bolognesi and Ledford, the cutoff level of 7 parts per billion (ppb) for Co or Cr has been generally recommended to guide treatment (Bolognesi and Ledford 2015). However, lower cut-offs (<3-5 ppb) have been recommended for more accurate risk stratification, as summarized in the Consensus Statement of the American Association of Hip and Knee Surgeons, the American Academy of Orthopaedic Surgeons, and The Hip Society (Hart et al. 2011). According to the United Kingdom's Medicines & Healthcare products Regulatory Agency (MHRA), "MARS MRI scans or ultrasound scans should carry more weight in decision-making than isolated blood metal levels alone" noting that "Rising blood metal levels may indicate potential for soft tissue reaction." This information has recently been summarized on the FDA website.[10] In addition to the absence of clear criteria for relevant serum metal ion levels, there is also confusion

[10] https://www.fda.gov/medical-devices/implants-and-prosthetics/metal-metal-hip-implants

regarding other testing for immunological responses to metal implants. Both patch testing and lymphocyte transformation testing (LTT) have been suggested as screening tools for potential biologic responses to metals (Eftekhary et al. 2018). Recent studies, however, have shown these tests to be of limited clinical value. Granchi et al. noted that there was insufficient data to determine that a positive patch test represented a true metal allergy in patients who have had a total joint replacement, and was unable to discriminate between stable and failed arthroplasty (Granchi et al. 2012). Another study showed that in 161 Total Knee Replacements (TKRs) with preoperative positive patch tests, subjects had no increase in complication, reoperations, or revisions compared with matched controls with a negative patch test (Bravo et al. 2016). Yang et al. in a review of the clinical relevance of the LTT provided a retrospective review of 27 well-fixed aseptic TKRs revised due to persistent pain and suspected metal allergy (Yang et al. 2019). They noted that "LTT results alone were insufficient for the diagnosis of TKA failure due to an immune reaction. A positive LTT may not indicate that an immune reaction is the cause of pain and stiffness post-TKA. The role of LTT in assessing TKA failure from an immune reaction needs further investigation." Schneiderman et al. failed to show any correlation with LTT results and periprosthetic TKA tissue reaction (Schneiderman et al. 2019). Thomas noted that there is currently a lack of an established sensitivity and specificity of the test (Thomas 2013). Eftekhary et al. summarized the use of these two tests by stating "The ability of these tests to diagnose disease and predict outcomes has not yet been demonstrated." (Eftekhary et al. 2018) While other tests to establish adverse metal responses have been suggested (Lachiewicz, Watters, and Jacobs 2016), establishing a diagnosis of this response that can accurately guide treatment remains elusive.

7.5.2 Cardiac and Endovascular Implants

Cardiac devices with metal elements include coronary and other arterial stents; patent foramen ovale (PFO) occluders; pacemakers, and ICDs (Implantable Cardioverter Defibrillators). Contact dermatitis and delayed hypersensitivity-type reactions have been reported in all these metal cardiac devices and cardiotoxicity was reviewed in Section 7.4.1 above.

7.5.2.1 Stents

Vascular stents are expandable mesh tubes most commonly made from metal with a drug/polymer coating. These devices are designed to prevent vessel recoil by preserving the patency of the vascular lumen; they keep the walls of a blood vessel from becoming clogged or collapsing. Stents can be classified by their mechanism of expansion (self-expanding or balloon expandable), their composition (stainless steel, cobalt-based alloy, nitinol, inert coating, gold coating, active coating, no-coating, or biodegradable), and their design (mesh structure, coil, etc.). Metal alloys used for stents may include metals such as Ni, Ti, Cr, and Co.

7.5.2.1.1 Coronary stents

Following vascular stent placement, approximately 10–15% of patients develop a narrowing or closing of the stented vessel referred to as in-stent restenosis (ISR) and may require repeated revascularization at some time after implantation. There have been questions whether metal-induced reactions (not just hypersensitivity) to vascular stents can cause implant failure in the form of restenosis, but the interpretation of available published evidence is somewhat muddled by the variety of stents (bare metal *vs*. drug-eluting, metal composition, *etc*.), small cohorts, and technical challenges of testing for metal reactivity. Nevertheless, some case reports and studies suggested an association between ISR and Ni sensitivity per patch testing (Köster et al. 2000; Iijima et al. 2005; Svedman et al. 2009).

A clinical study of patients receiving stainless steel coronary bare-metal stents demonstrated a higher frequency of angiographically-determined ISR of the initial stent in those with a positive patch test reaction to Ni or Mo versus patients with negative patch test results. Patch testing for metal allergies was performed on 131 patients undergoing repeat angiography for suspected coronary restenosis approximately six months after receiving stainless steel alloy 316L bare metal stents. Of these, 10 patients (8%) had positive patch reactions, and all of them were found to have ISR (p = 0.03). In contrast, only 65% of the patch-negative group had restenosis. As a result, an "allergic reaction" to implanted metal was suggested as a trigger for restenosis (Köster et al. 2000).

In a retrospective study, Svedman et al. (Svedman et al. 2009) aimed to evaluate the relationship between coronary stent material, contact allergy, and restenosis. All patients (n = 484) were patch tested for Ni and Au reactivity then received either a bare metal stainless steel (316L) stent (n = 314 patients), the same stent that was electroplated with 99.9% pure Au (n = 146 patients), or both kinds of stents (n = 24 patients). Pre-existing patch test positivity to nickel was similar in both stent groups (13.1% in the Ni stent group and 9.6% Au stent group, p >0.3). The pre-existing patch test positivity to Au was also similar in both stent groups (32.5% in the Ni stent group and 39.0% Au stent group, p = 0.17). Overall, the frequency of ISR in Au-stented patients was significantly higher compared to Ni-stented patients (24.7% and 13.1%, respectively; p = 0.0016). In the Ni-stented group, there was no statistically significant difference in restenosis rate between allergic and non-allergic patients (17.8% and 12.3%, respectively). However, in the Au-stented group, there was a significant difference in restenosis rate between allergic patients and non-allergic patients (33.8% and 18.6%, respectively; p = 0.03). The Au-allergic patients with Au-plated stents had an increased degree of chest pain. When a multivariate logistic regression model where sex, age, and dental gold restorations was applied, a correlation (p = 0.04) between Au allergy, Au stent, and restenosis was demonstrated (Svedman et al. 2009).

Some studies also noted a possible association between Ni sensitivity and recurrent coronary ISR (Iijima et al. 2005; Saito et al. 2009). As reported by Iijima et al. (2005), the percentage of positive patch test results in patients having repeated coronary ISR was significantly higher than in those without recurrence of restenosis (39% vs. 12%; p = 0.02) and multivariate analysis further suggested that a positive patch test could be a significant predictor of recurrent ISR (Iijima et al. 2005).

Gong et al. (2013) carried out a meta-analysis of nine studies which evaluated the incidence of metal allergy in coronary patients with ISR vs. without ISR. An allergy to stent material was confirmed by patch testing, and ISR was identified by coronary angiography or other methods. A fixed-effect model based analysis showed that being allergic to stent material increased the risk of ISR (OR=2.65, CI: 1.82-3.82); a race-based subgroup analysis suggested a higher risk for Asian patients compared to Europeans (Gong et al. 2013).

However, some clinical studies did not find statistically significant relationships between having a metal allergy and ISR (Thyssen et al. 2011) or other adverse outcomes after stenting (Romero-Brufau et al. 2012). Thus, the association between metal stents, metal allergy, and stent failure or cutaneous reactions is not clear.

Mast cell-derived histamine may also contribute to the hypersensitivity reaction underlying Kounis syndrome, a coronary syndrome in thrombosis and failure of metal coated or plated cardiovascular stents (Kounis et al. 2012; Kounis et al. 2017).

7.5.2.1.2 Non-cardiac endovascular stents

Several case studies have reported cutaneous reactions after implantation of metal stents into non-cardiac arteries. (Giménez-Arnau et al. 2000) described a case of an elderly nickel-allergic patient who developed a severe pruritus accompanied by eczematous erythema on the lower limbs three 3 weeks after abdominal aortic aneurysm repair with a nitinol endograft. Her age made her an unlikely candidate for revision, but antihistamines and topical hydrocortisone tolerably managed her symptoms.

Two case reports have been published detailing a localized rash with pruritus involving the ipsilateral lower extremity after placement of a nitinol stent in the femoral artery. Both patients were found to be allergic to nickel and had resolution of symptoms with stent removal (Jetty et al. 2013; D'Arrigo et al. 2014). (Guerra and Kirkwood 2017) reported a case of a severe full-body desquamating macular-papular, pruritic rash developing within one month of implanting a nitinol stent into a popliteal artery after an embolus. The rash was resistant to high-dose oral prednisone and topical treatments. Subsequent patch testing was positive to nickel and the stent was explanted with resolution of most of the rash although the rash occasionally recurs. Another case report detailed the development of a diffuse rash consistent with a nickel reaction after placement of a stainless-steel stent placed in an iliac artery in a patient with a clinical history of developing an eczematous rash to sternal wires. While the white blood cell count was normal, the eosinophil fraction was 25.4% (a normal eosinophil fraction is 0 to 6%) suggesting a systemic allergic response or systemic hypersensitivity reaction (Univers et al. 2018).

7.5.2.2 Pacemakers and Implantable Cardioverter Defibrillators (ICDs)

Pacemakers help to manage abnormally slow heart rhythms while ICDs detect abnormally fast heart rhythms and deliver a small electrical shock to restore normal heartbeat. Newer-generation ICDs may also serve as a pacemaker (American Heart Association April 11, 2019). Implanted pacemakers and ICDs usually have two parts: a pulse generator placed near the collarbone and wires that are attached to the heart wall. Many generators are covered with a Ti capsule, while the alloy leads are insulated with polymers or silicone, and electrodes are typically made with platinum alloys. While many adverse reactions to cardiovascular devices are suspected to be due to Ni as a predominant cause, Ti (or its additives) has been implicated as the source for these reactions (Honari et al. 2008; Fage et al. 2016). In addition, the variety of other materials used in these devices complicates determining the true cause of the reaction (Shittu et al. 2015; Dogan et al. 2016)

Contact dermatitis and delayed hypersensitivity-type reactions have been reported with pacemakers and ICDs; most reported localized reactions included cutaneous eruption, pruritus, pain, erythema, and swelling at the site of pacemaker insertion (Kang et al. 2013) while some cases included sterile pocket erythema (Citerne et al. 2011), erosion, draining, and/or necrosis (Honari et al. 2008; Syburra et al. 2010; Dogan et al. 2016). These cutaneous reactions usually present within 2 days to 24 months after implantation and are often mistaken as surgical infections. Treatment with corticosteroids (topical or oral) may resolve the symptom;, however, in several cases, the symptoms recurred (Kang et al. 2013). In many cases, removal of the device, followed by a replacement with a device made from different materials, is needed to resolve the clinical problem.

7.5.2.3 Patent Foramen Ovale (PFO) Occluders

PFO occluders are used to close septal defects in the walls of heart chambers. Occluders are made of different materials and have different closure mechanisms.

In addition to local cutaneous reactions (Kim et al. 2008) (Belohlavek et al. 2013), occluders have been reported to be associated with systemic reactions presenting as chest discomfort, dyspnea (difficulty breathing), fever, edema, palpitations, migraines, and/or pericarditis with effusion (Honari et al. 2008; Rabkin et al. 2009; Spina et al. 2016). In one case, a patient with a known severe contact dermatitis to any metal jewelry presented with severe bronchospasm (Khodaverdian and Jones 2009). As in several other cases, her symptoms resolved only after removal of the implant; in other less severe cases, symptoms resolved after course(s) of corticosteroids.

Within a study of 46 patients evaluating the relationship between Ni hypersensitivity and unusual side effects after interatrial shunt device closure (Rigatelli et al. 2007), a cohort of nine patients who were patch test positive to nickel and underwent implantation; eight developed what the authors referred to as a post-procedure "device syndrome" characterized by chest discomfort, exertional dyspnea, and asthenia that began within 24 hours of the procedure. In one, the syndrome resolved spontaneously after 5 weeks; the other seven were treated with 10 mg/day of prednisone and 75 mg/day of Clopidogrel plus the usual dose of 100 mg/day of aspirin. All symptoms resolved after 1 week of treatment. The authors noted that none of the patch-test negative 37 patients who completed the procedure developed these symptoms.

7.5.3 Dental and Oral/Maxillofacial Devices

A variety of metals are used in dentistry. This includes precious metal alloys such as gold, platinum, silver, palladium, iridium, rhodium, osmium, and ruthenium and base metal alloys such as cobalt-chromium and nickel-chromium used to fabricate crowns, bridges, and partial dentures. Other metals used include nickel titanium and cobalt chromium nickel alloys for orthodontic arch wires, stainless steel alloys for preformed crowns and orthodontic brackets; titanium alloys for endosseous implants and bone fixation plates and screws; dental amalgam (mercury, silver, copper and tin) for tooth restoration; and cobalt chromium for temporomandibular joint (TMJ) implants. Except for TMJ implants, endosseous implants, and bone fixation plates and screws, most of these devices are not metal implants but are surface or external communicating devices. Dental amalgam is included in the discussion of metal implants because its use has been associated with increased mercury body burden ((SCENIHR) 2015) However, FDA has completed and posted a separate review of health effects of dental amalgams.

7.5.3.1 Temporomandibular Joint (TMJ) Implants

The bilateral TMJs, formed by the articulation of the condylar head of the mandible and the mandibular fossa and articular tubercle of the temporal bone of the cranium, are unique in that the two joints must function together as one unit. The fibrocartilage covered articulating surfaces are separated by an articular disk which splits the joint into two synovial joint cavities, and three extracapsular ligaments act to stabilize the joint during the initial rotation of the condylar heads, followed by translation where the condyle and meniscus slide forward and downward beneath the articular eminence (Kreutziger KL 1975).

Clinical conditions that may result in deformity/destruction of the TMJ include irreparable condylar fractures (trauma), joint ankyloses, dentofacial deformities, neoplasms, severe inflammatory and degenerative joint disease with condylar bone loss, as well as failure of autogenous grafts, may be addressed through partial or total TMJ replacement of the mandibular fossa /condylar head of the mandible implant(s) (Driemel et al. 2009). The history of TMJ surgical interventions also includes implantation of an intraarticular disc composed of polytetrafluoroethylene (PTFE) as a meniscus

replacement post discectomy, as a means to maintain vertical dimension of the jaw (Lypka and Yamashita 2007) . However, as the TMJ is a loaded joint under continuous movement, PTFE discs commonly fragmented resulting in an intense foreign body (giant cell mediated) reaction and significant loss of bone (Lypka and Yamashita 2007) and possible additional surgical procedures including partial or total joint replacement (Henry and Wolford 1993)**.**

In response to detection of significant history of failure with total or partial TMJ replacements, the FDA ordered all TMJ implant manufacturers to conduct 522 Postmarket Surveillance Studies[11] to help determine causes of TMJ implant failure. As of Spring 2019, these studies are showing that the most common reasons for subsequent surgical intervention include fibrous ankylosis, heterotopic bone formation, infection, and pain/swelling.

7.5.3.2 Endosseous Dental Implants, Dental Restorations, and Dental Appliances

Endosseous dental implants are used to replace teeth and restore chewing function by supporting dental restorations such as crowns or bridges. Endosseous dental implants are placed in the maxilla or mandible to replace the root and prepared crown portions of the tooth. Dental appliances have a variety of intended uses; for example, orthodontic wires are intended to assist in tooth movement as part of orthodontic treatment of malocclusion. Ni and Ti are commonly found in dental restorations and appliances such as crowns and orthodontic wires. Although Ti in endosseous dental implants, dental restorations, and dental appliances have been generally considered inert in terms of the interactions with the oral cavity, recent reviews of the literature suggest possible adverse reactions to various constituent metals including Ti (Siddiqi et al. 2011; Levi, Barak, and Katz 2012).

7.5.3.3 Bone Fixation Plates and Screws

Bone fixation plates and screws for use in the oralmaxillofacial areas are devices composed of titanium or titanium alloy that are intended to stabilize injured or congenitally deficient oral and maxillofacial bones. These devices share many of the same sensitivity concerns as titanium orthopedic fixation devices (Goutam et al. 2014).

7.5.3.4 Dental Amalgam

Dental amalgam, a filling material used to fill cavities caused by tooth decay, consists of a mixture of metals including liquid mercury (Hg) and a powdered alloy composed of silver, tin, and copper. Approximately 50% of dental amalgam (by weight) is elemental mercury. High levels of mercury vapor exposure may cause potential toxic effects endangering patients and dental professionals as well. However, the exposure to mercury from dental amalgam occurs mainly during placement or removal of amalgam restorations. After the placement, long-term exposure to the hardened dental amalgam usually results in a much lesser mercury release that is considered far below the current health standard (About Dental Amalgam Fillings, FDA[12]).

Exposure to dental amalgam may result in increased Hg levels, often in correlation with the number of personal or placed/removed dental amalgam fillings {Nicolae, 2013 #798}; (Yin et al. 2016); (Goodrich et

[11] For information on 522s see: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pss.cfm?s=t

[12] https://www.fda.gov/medicaldevices/productsandmedicalprocedures/dentalproducts/dentalamalgam/ucm171094.htm#risks

al. 2016). Among dental professionals, elevated Hg levels were associated with occupational hygiene behavior and certain hazardous habits (Goodrich et al. 2016); (Duncan et al. 2011).

Dental amalgam has been associated with hypersensitivity reactions, mostly attributed to mercury and manifested as allergic dermatitis (Kirshen and Pratt 2012), orofacial granulomatosis (Tomka et al. 2011), and oral lichenoid lesions (Gönen et al. 2016). Dental amalgam is also capable of causing "amalgam tattoos", i.e., asymptomatic dark macules on the oral mucosa which occur when amalgam particles are inadvertently implanted into oral soft tissues during dental procedures and which may be accompanied by histopathologically detectable foreign body reaction (Amano et al. 2011). Some isolated studies suggested possible systemic effects, linking dental amalgam exposure to possible neurological diseases such as Parkinson's (Hsu et al. 2016) and autoimmune conditions such as ASIA (Stejskal, Ockert, and Bjorklund 2013); (Alijotas-Reig et al. 2018). Pediatric studies on putative associations with neurodevelopmental outcomes due to personal or maternal exposure to dental amalgam mostly reported negative (Maserejian et al. 2012); (Watson et al. 2013); (Wright et al. 2012) or inconclusive (Geier 2009) evidence.

FDA has conducted periodic reviews of the amalgam literature to assess for new information concerning its safety. The latest review was conducted in 2019, for which a separate report has been prepared[13]. This report found no clinical evidence from controlled studies that would unequivocally support the causal associations between occupational or non-occupational exposure to dental amalgam and systemic adverse outcomes. However, the reliability of evidence from many currently available clinical studies was questioned by the emerging evidence on *in vivo* transformation of inorganic mercury into methylmercury (Uchikawa et al. 2016); (Martín-Doimeadios, Mateo, and Jiménez-Moreno 2017); (Li et al. 2019) and subsequent limitations of conventional approaches for distinguishing between inorganic Hg from dental amalgam and dietary methylmercury, which postulate urine and hair measurements as their respective indicators (Sherman et al. 2013); (Manceau et al. 2016). As a result, dental amalgam is included as a separate topic for the upcoming panel meeting(s) aimed to solicit input and advice for addressing potential safety issues of metal-containing medical devices.

7.5.4 Neurological Devices

A variety of devices used in neurological applications include Ni and its mixtures with other metals including aneurysm clips (used to prevent major arteries from rupturing); stent-assisted coils for embolization (to hold embolization coils in the aneurysm sac and support the artery); and flow diverters (high mesh density metal stents placed in the vessel to divert blood flow from entering the aneurysm sac). There are case reports of possible nickel-related adverse effects after aneurysm treatment recently reviewed in (Tsang, Nicholson, and Pereira 2018). In several cases, a focal neurological syndrome usually beginning two to four weeks after the implant has been reported (Terence Tan, Jin W. Tee, and Tiew F. Han 2014; Lobotesis et al. 2015; Shotar et al. 2016; Park et al. 2017). On MRI, the distinguishing characteristics of this syndrome include multifocal significant T2-hyperintense lesions suggesting edema. Most of the patients presented with neurological deficits, including seizure, limb weakness and speech disturbances. Not all these case reports included patch testing for allergy to Ni or other metals. As expected from earlier discussions, skin patch testing for nickel reactivity was positive for some of the patients (Schmidt and Goebeler 2015); (Lobotesis et al. 2015; Shotar et al. 2016; Park et al. 2017);

[13] Reference to the corresponding regulatory document will be updated/added once publicly available

however, in some patients, the clinical signs did not always correlate with the patch test negative results (Tan et al. 2014)(Park et al. 2017).

There are few studies that review the incidence of reactions to metal neurological implants in large cohorts of patients receiving neurological metal devices. In a retrospective review of 374 patients treated for brain aneurysms, two patients (0.5%) met their criteria for delayed non-ischemic cerebral enhancing lesions and only one of them had a Ni-positive patch reaction (Shotar et al. 2016). A recent chart retrospective (Wallace et al. 2019) reviewed 20 patients with self-reported cutaneous metal allergy—defined as itching, redness, or other signs or symptoms of dermatitis after skin contact with metals – who received a flow diversion device consisting of a braided, multi-alloy, mesh cylinder woven from cobalt-chromium-nickel and platinum/tungsten alloy wires and is used to support the vessel around the aneurysm. None of the patients reported a cutaneous allergic reaction after implantation and through the following six months.

7.5.5 Gastroenterological Devices

Metal stents are occasionally used in gastroenterology practice, especially in palliative (relief of symptoms without a cure) settings. Self-expandable metallic stents (SEMS), coated and bare metal are preferred for the first-line treatment of liver cancer, bile duct strictures and palliation of the narrowing of the esophagus due to cancer. In contrast, plastic stents are preferred for benign biliary strictures that require intervention to treat jaundice (yellowing of the skin), chronic blocked bile flow, and inflammation of the bile duct (Nam and Kang 2016). Likewise, self-expandable plastic stents are preferred for treatment of benign esophageal diseases (Sharma and Kozarek 2009). However, since patency for plastic stents is often short (roughly three months), metal stents are sometimes used instead.

While SEMS generally are not used for benign biliary and esophageal strictures, there are sporadic case reports of hypersensitivity (Esparaz and Ahmed 2017),(Khan et al.), manifested as contact dermatitis with itching and hives, as well as right upper-quadrant abdominal discomfort, nausea, fever, malaise (vague feeling of discomfort), and lassitude (weariness or listlessness).

7.5.6 Gynecological devices

7.5.6.1 Essure® Hysteroscopic Sterilization Device

This NiTi-based device is inserted transvaginally into the fallopian tubes and is intended to induce a moderate inflammatory response resulting in fibrosis and subsequent tubal occlusion. It should be noted that the device also contains PET fibers. Based on the reported number of products sold, approximately 750,000 women worldwide have undergone Essure hysteroscopic sterilization (Walter et al. 2017). About ten years after the FDA's approval of Essure in 2002, concerns over its safety started to rise, mostly driven by Medical Device Reports (MDRs) submitted to FDA's Manufacturer and User Facility Device Experience (MAUDE) database. In 2015, FDA reconvened the Obstetrics and Gynecology Devices Panel[14] and per the Panel's recommendations, ordered Bayer to conduct a 522 Postmarket Surveillance

[14] For more details on the Obstetrics and Gynecology Devices Panel meeting, see Essure® Permanent Birth Control; accessed March 31, 2017.

Study, which was to compare women with either Essure or laparoscopic tubal sterilization (PS160001[15]), including evaluations of systemic symptoms which had been reported to FDA. In April of 2018, the FDA restricted sale and use of Essure[16], and Bayer announced the halt of sales in the U.S. by the end of 2018.

As summarized by the American Association of Gynecologic Laparoscopists[17] (AAGL), Essure requires training to achieve the proper skill set for ideal placement, a backup method of birth control until the device becomes effective, and reliance on the follow-up confirmation test to confirm proper placement and/or tubal occlusion. In some studies comparing Essure® to tubal ligation, Essure® was associated with lower risks of unintended pregnancy (Fernandez et al. 2014) and complications experienced were described as more minor in nature (Ouzounelli and Reaven 2015). According to an Italian 11-year survey, only a few women (9/1,968) experienced severe post-Essure pain necessitating device removal (Franchini et al. 2017). The findings of a Phase III multicenter international study (Chudnoff, Nichols, and Levie 2015) supported tolerability of Essure, reporting that the majority of adverse events observed during the 5 years of follow-up were "mild" or "moderate" in severity.

However, overall real-world performance of Essure has been hindered by many complaints (Bahk et al. 2015; Yunker et al. 2015) not all of which were attributable to improper placement or other procedure-related technicalities. Despite a number of clinical reports on migration of an appropriately placed Essure device (Rezai et al. 2015), very few publications discussed peri-insert tissue changes (Ricci G 2014) as a possible evidence of the exaggeration of the expected macrophage-mediated inflammation and foreign body response (Valle, Carignan, and Wright 2001) which constitute Essure's mechanism of action.

Pelvic pain was the most commonly reported complaint, although the reports of new-onset pain (Chudnoff, Nichols, and Levie 2015) and worsening of a pre-existing pain (Kamencic et al. 2016) as well as pain requiring Essure removal (Arjona Berral et al. 2014) were relatively rare. Essure-related pelvic/abdominal pain was emphasized in the reports collected via MAUDE database (Dhruva, Ross, and Gariepy 2015; Zuckerman and Doamekpor 2015) and social media (Bahk et al. 2015).

In patient outreach based on the FDA-provided MedWatcher app adopted by the Facebook community "Essure Problems" (Bahk et al. 2015), *serious* (*e.g.,* hospitalization) and *important (e.g.,* device dislocation, and salpingectomy) adverse outcomes were reported by 77.6% and 44.3% of women, respectively; reported Essure-associated events also included heavy bleeding, fatigue, hair loss, alopecia, depression, loss of libido, and allergy to metals (primarily Ni). In some cases, symptoms attributed to Essure persisted after device removal (Brito et al. 2015). FDA has also received numerous patient reports noting the development of other systemic signs and symptoms, including but not limited to muscle ache/pain/weakness, joint pain, weight changes, insomnia, Raynauld's, memory loss, and cognitive changes. Some implanted women also state that they received a new autoimmune diagnosis (e.g., rheumatoid arthritis, systemic lupus erythematosus) after insertion.

[15]For more details on the PS 522 Essure study (PS160001), see Essure® 522 Postmarket Surveillance Studies; accessed March 31, 2017.

[16]https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/EssurePermanentBirthControl/ucm452254.htm

[17] The Board of Directors of the AAGL formed a task force of leaders in the field of minimally invasive gynecology to provide a document outlining the current status of Essure hysteroscopic sterilization (Bayer, Whippany, NJ).

Patients with previous diagnoses of any chronic pain conditions such as fibromyalgia were more likely to report post-Essure pain (Yunker et al. 2015). Symptoms suggestive of systemic/autoimmune conditions were mentioned by some Essure patients who presented at the 2015 Obstetrics and Gynecology Devices Panel meeting. In a small study on women who experienced post-Essure pregnancy, some participants (4/103) reported an autoimmune-type condition either before or after an Essure procedure (Sills et al. 2015). However, no significant difference in the history of diagnoses for autoimmune (as well as thyroid) disorders was found in the recent large study comparing hysteroscopic (Essure) and laparoscopic sterilizations (Bouillon et al. 2018). Despite the existing patient-reported outcomes, published clinical evidence clearly demonstrating a causative role of Essure in *de novo* autoimmune condition(s) was not found in the literature search conducted for preparation of this paper.

Unlike the lack of definitive evidence on autoimmune conditions, there is evidence linking Essure to Allergic Contact Dermatitis (ACD), conventionally attributed to the Ni-induced (delayed, type IV) reaction and described as localized or Systemic Contact Dermatitis (SCD), including eczema and pleomorphic rash (pruritic, urticarial, maculopapular, *etc.*) (Al-Safi et al. 2011; Zurawin and Zurawin 2011; Lane, Tyson, and Thurston 2016). In rare cases, the Essure-related SCD involved the genital region and was described as ''baboon syndrome'' (Bibas et al. 2013). Patch testing was recommended only in cases when a woman with the Essure *in situ* experiences SCD-like symptoms and no other possible cause can be found (Lane, Tyson, and Thurston 2016). As an explanation why fewer women exhibit symptoms of Essure-related SCD compared to what is expected based on a history of ACD and a positive patch test (Lane, Tyson, and Thurston 2016), Bergman et al. (2016) underscored the difference between ACD and Systemic Nickel Allergy Syndrome (SNAS) (Bergman, Goldenberg, and Jacob 2016), a Ni-specific subset of SCD that may occur in persons who might have been sensitized to Ni via different routes (e.g., diet) and which includes extra-cutaneous symptoms (e.g., gastrointestinal, respiratory, neurological, etc.) (Pizzutelli 2011).

However, the actual reported incidence of Essure-associated Ni sensitivity was low and positive test results did not necessarily correlate with clinically significant reactions (Adelman, Dassel, and Sharp 2014). The recent survey involving 1,913 women with Essure identified Ni hypersensitivity in only 6 cases (Franchini et al. 2017). Only 2 cases with Ni allergy-like symptoms (*e.g.,* genital pruritus, erythema, and papular urticarial rash) were identified in a retrospective study on 4,306 Essure procedures (Povedano et al. 2012), where >700 cases of Ni allergy should have been expected, according to the authors' comparison using 17% as an estimate for Ni allergy in the general population (Thyssen et al. 2010). In a study on 169 women who underwent Essure sterilization and completed patch testing before and after (3 months) procedure, no significant changes were reported regarding Ni positivity (29% pre- and post-insertion) or allergy symptoms (Siemons, Vleugels, and van Eijndhoven 2017). However, it remained unclear whether these data support the authors' conclusion that "Essure sterilization likely is not related to nickel sensitization", or whether they indicate that patch testing is insufficient for accurately describing the rate and scope of Essure-attributable events.

The inexplicably low patch testing-based estimates of Ni allergy (or sensitivity) among Essure patients compared to the general women population raise doubts about their statistical validity as well as their pathogenetic relevance to the entire spectrum of Essure-related adverse outcomes. Based on a total of 63 reports of Essure-related "allergy" cases and corresponding Essure sales data, Essure-related Ni hypersensitivity was estimated only at 0.014%; no possible explanation, however, was provided for a drastic difference from the Ni allergy levels (18%-24%) reported in the general women population (Zurawin and Zurawin 2011; Adelman, Dassel, and Sharp 2014). As commented by Lane et al. (2016), if

all expected individuals with a Ni allergy would have had a reaction after the Essure procedure, the MAUDE analysis by Zurawin and Zurawin (2011) should have resulted in 72,000 to 96,000 cases (Lane, Tyson, and Thurston 2016). Taken together, these data might suggest that Essure-related "hypersensitivity" is not necessarily allergic by nature and that a true allergy is rarely a cause for device removal (Zurawin and Zurawin 2011), thus implying different – non-allergic – pathogenetic mechanisms underlying pain and other Essure-attributed adverse outcomes. However, the significant limitations of a passive reporting system such as the MAUDE database should be considered in interpreting the authors' conclusions.

7.5.6.2 Copper-containing intrauterine devices (IUD)

Although the exact mechanism of action of copper-IUDs is difficult to elucidate, these reversible contraception devices are characterized as "functional spermicides" designed to prevent the formation of viable embryos by inducing local change in the endometrium (Ortiz and Croxatto 2007).

Copper (Cu) ions released from a copper-containing IUD (which can be made from up to 99.9% pure Cu wire) are thought to exert contraceptive effects via inflammatory response that is usually limited to the uterus and genital tract, but in some cases, may affect distant organs (Ortiz and Croxatto 2007).

Similar to NiTi-based Essure, copper-IUDs have been reported to be associated with pain and heavy bleeding and in rare cases, with uterine perforation and device expulsion/migration (Nelson and Massoudi 2016). Suggesting the role of hormonal factors in the IUD-related tissue changes and subsequent perforation, a meta-analysis on copper-IUDs found that uterine perforation with IUD insertion was 6 to 10 times more likely in breastfeeding vs. non-breastfeeding women ('Intrauterine Copper Contraceptive' 2006). In the large EURAS-IUD 5-year extension study (Barnett et al. 2017), the overall perforation rate for copper-IUD users was estimated as 1.6 per 1000 insertions (95% CI: 0.9-2.5), which was lower than the corresponding estimate for users of hormone (levonorgestrel)-releasing IUDs. In rare cases, IUD-related perforations were reported to result in injuries to intra-abdominal and pelvic structures, such as in the case report on a copper-IUD that was located in the abdominal wall, resulting in a foreign body granuloma and mimicking acute appendicitis (Ansari et al. 2009).

No difference in serum Cu levels was found in an earlier study on women using specific copper-IUDs up to one year (Arowojolu, Otolorin, and Ladipo 1989). However, in a study of different product, IUD users, regardless of age or length of use, had blood Cu levels above normal concentrations and significantly higher compared to non-users (De la Cruz et al. 2005).

Some reports on copper-IUDs described reactions suggesting involvement of adaptive immunity. There have been at least 5 documented cases where women with copper-IUDs developed systemic ACD with metal sensitivity confirmed by patch testing and symptom resolution upon device removal (Teo Wendy and Schalock 2016). As an example, Purello D'Ambrosio et al. (1996) reported a case of copper-IUD-related endometritis and vulvovaginitis accompanied by treatment-resistant urticaria and angioedema. Patch testing and lymphocyte-stimulating test (LST) showed strong positivity to Cu sulfate and the Cu spiral applied to the patient's forearm also provoked a positive reaction with erythema, itching, and rash; device removal resulted in complete symptom resolution (Purello D'Ambrosio et al. 1996).

Some small studies explored potential immune and inflammatory markers in relation to copper-IUDs. In a study on a copper versus non-copper IUDs, women using the copper-based device for <1 year had higher increases of serum acute-phase reactants and immunoglobulins G and M (Shaarawy et al. 1981).

Circulating IL6 levels were elevated in 20% of women using another copper-IUD for 10-24 months (Woolley et al. 1996); however, it remained unclear whether the increased circulating levels of this proinflammatory interleukin was a result of "overspill" from local inflammatory response or an indication of possible IUD-related systemic immune activation. A copper-IUD was also reported to precipitate familial Mediterranean fever (FMF) attacks one week after insertion in a 23-year-old Turkish woman who was diagnosed with FMF at 12 years old and was symptom-free on colchicine treatment for at least 4 years (Kurultak et al. 2015); the clinical reoccurrence of an autoinflammatory disease such as FMF suggested to the authors that a copper-IUD may trigger a systemic inflammatory response in the presence of predisposing factors such as a mutation (M694V) in the autoinflammation-causing gene (MEFV).

7.6 CONCLUSIONS

With the increasing awareness and concerns about possible reactions to constituent metals, a more nuanced evaluation of the entire spectrum of device/biomaterial-specific ARMDs is needed as a prerequisite for developing adequate diagnostic and therapeutic measures aimed to improve long-term implant safety. Management of the asymptomatic patients with few risk factors for ARMD is currently limited to monitoring of implant function and corresponding patient outcomes. Identification of at-risk patients and the therapeutic management of symptomatic patients remains controversial, in part due to the failure of currently available testing methods, such as skin patch or metal ion levels, to definitively identify the patients at high risk for implant failure. A more systematic research approach incorporating all possible clinical manifestations and underlying pathogenetic mechanisms is needed for enabling a timely detection and preventive treatment of adverse outcomes pertaining to implant reactivity.

8 SCREENING AND DIAGNOSTIC TOOLS

Various tests and techniques can be used to understand the host body's reaction to a metal implant however, at this time our 'toolbox' is limited. The best developed tests we have available include tests that measure metal levels in the blood; tests that can measure some aspects of the immune system by testing reactions in the skin (patch testing) and in a lab test (lymphocyte transformation test); and specialized imaging techniques like microscopic histology, MRI, and ultrasound.

Although many of these techniques have the advantage of being non-invasive, all the tests and imaging techniques have challenges with biological and measurement variability that will be challenging to overcome. Most techniques do not always have a clear relationship between a tests' results and the implant's status. Likewise, these techniques are not able to predict whether an implant will fail in the patient.

Our goal is to have a full set of effective tools that will predict adverse effects before implantation, for quantifying and visualizing adverse effects, or can quickly identify problems before they are clinically significant.

8.1 INTRODUCTION

The first step to creating an effective diagnostic or screening tool is to have consensus among the scientific field on desired endpoints that are clinically meaningful. This section will review the current state of screening and diagnostics related to pre- and post-operative assessment of patients with metal implants. Gaps within existing technologies and future opportunities will also be identified and discussed.

8.2 Diagnostic Tests for Evaluation of Metal Sensitivity

An effective screening tool for metal implants would strike an optimal balance between sensitivity (to enable detection before a serious adverse event) and robustness (to promote confidence that the signal detected is real). Currently, there are only a few diagnostic tests that are used for measuring a patient's immunological response to metal implants. These tests generally seek to determine the levels of specific metals in the patient's body and evaluate their sensitivity type responses to metal debris. The methods for conducting these assessments and the limitations and advantages of each are described in the sections that follow.

8.2.1 Patch Testing

The American Contact Dermatitis Society (ACDS)) (Schalock et al. 2016), and many researchers have historically used patch testing for detecting systemic type IV hypersensitivity reactions to metal implants (Teo and Schalock 2017). The ACDS carefully qualifies the patch test reaction not as a textbook type IV hypersensitivity reaction but uses the term "metal hypersensitivity reactions (MHRs)" to "approximate the innate and adaptive immune reactions that are described in the local and regional environment of a metallic implant" because it states "(a)lthough the patch test does not completely evaluate all mechanisms of hypersensitivity, the epicutaneous patch test seems to be the best test for the evaluation of potential metal reactions, both before and after implantation." Despite the prior assertion, the immunological relationship between patch testing and the systemic and/or local immunological responses systemically is unclear and the literature regarding this relationship is conflicting (Schalock et al. 2016; Teo and Schalock 2017) .

8.2.2 Description of Patch Test

Reliable, consistent technique is important for correctly assessing a patient using patch testing. Recommended patch test procedures are available from several sources. For example, Fonacier (Fonacier 2015) outlines a practical guideline for patch testing, as does Johansen et al. (Johansen et al. 2015).

Most patch test formats use small square or round plastic chambers covered by impermeable hypoallergenic tape, allowing close contact between the skin and the allergen in the chamber. Different loading chambers are available in different sizes, shapes, and materials. Several other patch testing systems are also available, and patch test allergens can be obtained from numerous commercial sources (Fonacier 2015).

The chambers are filled with various substances in an inert substance, often petrolatum or water. Paper filters are soaked with aqueous solutions and placed in the chamber. Typically, several substances or a series of concentrations of a single substance are tested at the same time. For example, a metal ion panel might include patches of 2.5% nickel sulfate in petrolatum; 0.25% potassium dichromate in petrolatum; 1.0% cobalt chloride; and 10% titanium dioxide in petrolatum (Schalock et al. 2012). Schalock et al. (2012) and Honari et al. (2008) recommend metal compounds and concentrations for a baseline series and an adjunctive metal series in addition to testing the specific substances in the implant so important rarer allergens are not missed (Honari et al. 2008; Schalock et al. 2012). Many (82%) dermatologists (and the ACDS) recommend including glue components and antibiotics in the test panel as they can also cause allergic reactions in patients with metal implants (Schalock and Thyssen 2013; Schalock et al. 2016).

Patch tests are usually applied to the upper back for practical reasons – it offers a flat surface for the test chambers and is less often affected by skin diseases and sun exposure (Johansen et al. 2015). There are known variations in skin reactivity between different parts of the body (reviewed in Johansen et al. 2015). Therefore for comparability and standardization, it is important to use the same anatomical site for each subject throughout and between studies if possible (Johansen et al. 2015).

Test chambers are left on the skin for a period of time, usually 48 hours, (Fonacier et al. 2015) (Schalock et al. 2016)) although the European Society of Contact Dermatitis (ESCD: Johansen et al 2015) has stated that there was no evidence for general superiority of occlusion for one day or two days. When the test is removed, the skin under the squares are assessed for reaction to the substance in the chamber. The test is read by visual inspection and palpation of the site for redness (erythema), swelling (infiltrate), papules, and vesicles (fluid-filled bumps). The reactions range from negative (-) to extremely positive (+++) and are scored using the globally acknowledged (Fonacier et al. 2015); (Johansen et al. 2015); (Schalock et al. 2016) International Contact Dermatitis Research Group (ICDRG) scale (Fregert 1981). The scale also includes a category for evaluating an irritant reaction, a reaction to the test substance without allergic characteristics and a 'doubtful' category of mild or patchy redness without swelling. It is notable that both reactions can be mistaken for a true allergic response (Svedman et al. 2012; Fonacier et al. 2015) .

The test should be re-read at 72 or 96 hours after the initial application to evaluate late arising reactions (Fonacier et al. 2015) (Johansen et al. 2015; Schalock et al. 2016). Metals, including nickel sulfate, cobalt chloride, and potassium dichromate, are often associated with delayed peak reactions which can occur as late as six to seven days after the initial application (Fonacier et al. 2015). Differentiating between a mild allergic reaction and a 'doubtful' or irritant reaction is the greatest cause of misinterpretation of patch testing (Fonacier 2015). Often, irritant reactions will diminish or disappear by 96 hours while true allergic responses tend to increase in severity for several days (Fonacier 2015) (Johansen et al. 2015).

Test readers are cautioned to consider false positive and false negative reactions (Fonacier et al. 2015; Johansen et al. 2015). False-positive reaction can result from various causes such as the use of irritants or allergic substances at potentially higher concentrations, pressure from the filling chamber, "angry back syndrome" where large true positive reactions spread into other patch testing areas, or patch testing on skin with active dermatitis.

The frequency of false-negative results for patch testing for metal ions is unknown, however it has been estimated to occur in up to 30% of patients patch-tested after occupational exposure (Fonacier 2015). False-negative reactions could be due to use of an inadequate allergen concentration needed to elicit a response; inability of the vehicle to release enough allergen; reduced skin responsiveness because of prior ultraviolet light exposure (i.e., sun, tanning bed); concomitant immunosuppressive therapies; or methodological testing errors such as insufficient occlusion, or a failure to perform delayed readings (Fonacier et al. 2015).

The choice of form of the metal used for patch testing may also have important implications for determining a patient's reactivity ((Siemund et al. 2017; de Graaf et al. 2018)). Titanium is often thought to be hypoallergenic, however clinical experience with dental and orthopedic implants suggests that Ti allergy occurs more often than patch testing would indicate. In a retrospective chart review of 458 patients who underwent patch testing with at least one of five different titanium salts, Graaf et al. (2018) found that at least one of the titanium salts caused a positive result in 5.7% (n = 26) of the

patients (de Graaf et al. 2018). Titanium (IV) oxalate hydrate (n = 216, 7.9% positive) had the highest yield while the most commonly studied titanium dioxide (n = 329, 0.9% positive) had the lowest yield of positive reactions. Of the 26 positive samples, 15 were from patients with titanium implants (3 dental, 10 orthopedic or surgical, 1 neurostimulator, and an insulin pump). Erythema, dermatitis (overlying the implant or elsewhere), and local swelling were identified in all the patients.

8.2.2.1 *Patch testing reproducibility*

Despite its frequent use, patch testing has not always been reproducible. Sources of variability in diagnostic patch testing have been summarized by (Ale and Maibach 2004). They summarize the variables by materials (e.g., type of patch test system, different concentrations of some allergens, etc.); methodology and technical drawbacks (e.g., interpretation of the responses, application and reading times, etc.); and biological (hormonal influences, weak or doubtful responses, poor absorption through the skin, etc.). Many of these influences have been examined, but the many variables make it difficult to fully interpret the responses, as seen within patient and between readers below. The reproducibility of other variables, including between-allergens; between-test systems; and between manufacturers of allergen, will not be discussed below as they are beyond the scope needed to discuss the predominant areas of uncertainty regarding reproducibility.

8.2.2.1.1 Within-patient reproducibility

Patch testing's ability to give consistent results on the same patient, reproducibility, has been questioned. In trials evaluating whether duplicates of allergens applied symmetrically to the left and right sides of the patients' upper backs have shown differing concordance in obtaining double-positive or double-negative results, older studies have shown large variations in the reproducibility rate of positive responses, ranging from 56.2% to 95.8% (Ale and Maibach 2004).

More recent studies have been more consistently showing high reproducibility or concordance because of careful attendance to decreased methodological variability and careful patient inclusion (e.g., (Ale and Maibach 2004; Bjork et al. 2017) , (Siemund et al. 2017)). These studies also note that almost all the discrepant results are between the weak reactions and the negative reactions. Björk et al. (2017) showed excellent reproducibility for the very strong (3+) reactions, however, as the reactivity decreased, reproducibility also decreases in a "dose–response manner" when the patient's previous reactivity had been low, e.g., a + reaction. In other words, strong reactions are reproducible within that individual at that time, but it is difficult to reproduce low reactions and differentiate them from non-allergic reactions even in the same patient during the same test.

Evaluations of the long-term reproducibility are complicated by the loss of positive patch test reactions over time. Several longitudinal studies have analyzed the reproducibility and variation in patch test reactivity to metal salts such as nickel (Hindsen, Bruze, and Christensen 1999), cobalt (Rystedt 1979), gold (Bruze, Bjorkner, and Moller 1995), and aluminum (Siemund et al. 2017) and have found varying test reactivity over time, including finding negative reactions in previously positive patients. Hindsén et al. (1999) reported varying test reactivity over time, including negative reactions, after repeated patch testing of nickel-allergic and female patients (Hindsen, Bruze, and Christensen 1999). In a recent study (Siemund et al. 2017), 21 adults who had previously reacted positively to aluminum were patch tested with equimolar dilution series of aluminum chloride hexahydrate and aluminum lactate, four times over a period of eight months. Four of the patients had a negative reaction throughout the study. In the other 17 patients, the intensity of the reaction varied over time and in both aluminum salts. Fifteen of 21

participants did not react to aluminum lactate on one up to all test occasions and 11 of 21 participants did not react to aluminum chloride on at least one occasion. The authors were not able to determine whether the loss of reactivity is a true immunological response or because of previously discussed technical testing challenges; however, they do suggest that utilizing patch testing for evaluating metal implant status may be contraindicated.

8.2.2.1.2 Between-observer reproducibility for patch testing

An interesting study (Svedman et al. 2012) explored the inter-observer variability in patch testing reading. Eleven dermatologists evaluated six patients that had been tested with a panel of substances, including nickel sulfate and palladium chloride, in the same day. Their readings were compared to a 'gold standard' senior dermatologist. The dermatologists showed good agreement at differentiating between an allergic reaction and a non-allergic value that had been established by the senior dermatologist (kappa value = 0.73); however, if all different reaction types (including 'doubtful' and irritant reactions) were included, the kappa value dropped to 0.48. The study emphasized the difficulty of reproducibly evaluating doubtful and irritant reactions and establishing the distinction between doubtful and weak positive reactions and allergic reactions

High reproducibility is possible with experienced readers and appropriate test materials; strong reactivity also increases the reproducibility. However, it is not clear how reproducible patch testing is in routine, clinical use where the multitude of variables may interfere with patient results.

8.2.2.2 *Advantages and potential adverse effects of patch testing*

Patch testing has the advantages of a well-established, standardized methodology; a wide variety of metal compounds available for evaluating reactions to substances; a reasonable cost; and is non-invasive.

Potential adverse effects of patch testing include normally mild and localized irritant reactions such as, tape irritation, hyper- or hypopigmentation, and pruritus. Some of these reactions may persist for up to several weeks. Gold chloride and palladium tetrachloride are "notorious" (Johansen et al. 2015). Although possible in theory, allergenic sensitization by patch testing is uncommon (Johansen et al. 2015). The ESCD defines patch test sensitization as a positive patch test reaction generally beyond 2 weeks after an initially negative response at the same site that can be confirmed by repeat patch testing. No metal is included among the several allergens known to carry some risk of patch test sensitization (Johansen et al. 2015).

8.2.2.3 *Regulatory aspects of patch testing*

The Thin-Layer Rapid Use Epicutaneous Patch Test (T.R.U.E Test, Mekos Laboratories AS) is the only licensed patch test in the U.S. (FDA 2014). The kit includes three sticky bandages pre-loaded with allergens and allergen mixes. Of the 35 allergenic substances in the licensed panels, the following metals are included: 200 mcg/cm^2 of nickel sulfate hexahydrate, which corresponds to 36 mcg of nickel per patch; 54 mcg/cm^2 of potassium dichromate, which corresponds to 15.7 mcg of chromium per patch; 20 mcg/cm^2 of cobalt dichloride hexahydrate, which corresponds to 4 mcg of cobalt per patch; and 75 mcg/cm^2 gold sodium thiosulfate, which corresponds to 23 mcg/patch (FDA 2017).

8.2.2.4 *Testing Recommendations by Clinical Societies*

The ACDS (Schalock et al. 2016), the American Academy of Allergy, Asthma, and Immunology (AAAAI) (Johansen et al. 2015) and the ESCD (Johansen et al. 2015) do not recommend routine preimplant patch testing, although they state that it might be prudent to test a patient that strongly believes they are metal allergic. They base this suggestion on humanistic and medicolegal concerns rather than scientific findings.

Neither the ACDS (Schalock et al. 2016) nor the ESCD (Johansen et al. 2015) recommend patch testing for patients that are symptom free after implantation. However, they find patch testing is appropriate for patients with chronic unexplained issues such as implant loosening or failure after infection and biomechanical causes have been excluded. Schalock et al. (2015) note that while an implanted device can cause sensitization, a positive metal test does not prove causality of symptoms and that patch testing is only one of several elements to be considered in the evaluation of an implanted device.

Although there are many cleared assays for specific allergens (*e.g.*, pollens, foods, latex, etc.), there are no cleared allergy (type I)-based IVD assays specific for metals (nickel, chromium, cobalt) and the ability of metals to act as conventional allergens capable of inducing type I (i.e., atopic and/or anaphylactic) reactions is extremely questionable.

8.2.3 IVD Measurement of Metal Ions in Body Fluids

While there are no cleared or approved FDA tests, many laboratories offer determination of metal concentrations in biofluids as CLIA high complexity tests. These tests measure metal concentration using quantitative inductively coupled plasma-mass spectrometry (ICP-MS) and are indicated for evaluating occupational exposure and poisoning, rather than responses to metal implants.

While several other sections discuss the clinical utility of metal ions, this section discusses how metal ions are currently most commonly measured and provides an overview of some of the important analytical challenges associated with this technique. For additional information see sections: *Systemic Toxicity*; 5.4; 5.4.4.

8.2.3.1 *Measurement of metal ions*

Inductively coupled plasma mass spectrometry (ICP-MS) is the most widely used method today for determination of metal concentrations in both biological and inorganic samples. The instrument vaporizes a sample into ions then injects them into a mass spectrometer. The mass spectrometer separates and detects the ions according to their mass to charge ratio, and measures the analyte concentration by mass fractionation, providing a very sensitive quantitative method for analyte detection. ICP-MS's strengths include: simultaneous detection of many elements or ions; a low detection limit; and wide linear calibration range (reviewed in (Bolann et al. 2007; Ring et al. 2016) (Matusiewicz 2014)).The most significant challenge of ICP-MS is the potential for analytical interference by atomic or polyatomic species having the same mass/charge ratio as the target analyte. Relevant target metals that may be affected by such interferences include: chromium (as isotope ^{52}Cr), cobalt (as ^{59}Co), and nickel (as ^{60}Ni) (Case et al. 2001); (D'Ilio et al. 2006); (Ring et al. 2016). Measurement of Ti is particularly challenging (Swiatkowska, Martin, and Hart 2019). These interferences can affect analytical results if not properly removed or corrected and although the many specialized ICP-MS techniques used to reduce interference are beyond the scope of this paper, they are reviewed in (D'Ilio et al. 2011) and (Ring et al. 2016). Specialized methods with improved analytical sensitivity can allow ultra-trace

elemental analysis in highly complex matrices to be reliably performed and facilitate determination of the relevant levels for implanted patients however this area continues to evolve.

8.2.3.2 *Regulatory aspects of metal ions*

There are regulations in the Code of Federal Regulations (21 CFR §862) for testing levels of several metals; most of these tests are Class I and do not require pre-market evaluation. There are no regulations pertaining to testing levels of nickel, chromium, or cobalt. Apart from lead level determination, there are no cleared or approved FDA tests for metal levels. Several laboratories offer determination of metal concentrations in biofluids as CLIA high complexity tests. These tests are indicated for evaluating occupational exposure and poisoning but are often also used to measure metal ions from patients exposed to metal implants.

8.2.3.3 *Pre-analytical challenges concerning metal ions*

Regardless of how metal ions are measured, contamination is a significant concern when testing for very low concentrations. Careful elimination of contamination is critical to generating high level clinical or research results. Some, but not all, potential sources of error that can arise during collection, storage, or processing of samples that may significantly affect the test result are discussed below.

8.2.3.3.1 Sample collection

Stainless steel needles have been found to increase the concentrations of Ni and Cr during sampling (Cornelis et al. (1996); (Case et al. 2001). Several authors recommend the use of metal-free catheters after the initial puncture as well as discarding several milliliters of blood to diminish the chance of contamination (Cornelis et al. 1996; Case et al. 2001).

8.2.3.3.2 Collection tubes

Because of potential manufacturing contamination by other metals, several manufacturers market fluid collection tubes specifically for trace element analysis as well as some tubes certified for specific elements. Contamination may also originate from the tube stoppers, e.g. Zn; from the anticoagulant; or even from the container material, such as Al, in glass (Matusiewicz 2014). In addition, metals can be adsorbed by the sample tube. Many anticoagulants are either polyanions (e.g. heparin) or metal chelators (e.g. citrate) and therefore have a high affinity for contaminating metal ions (Cornelis et al. 1996). (Afolaranmi et al. 2010) found that the extent of Cr(VI) ions partitioned into red blood cells (RBCs) when collecting blood is significantly decreased by the anticoagulant ethylenediaminetetraacetic acid (EDTA), compared to sodium citrate or sodium heparin. Good laboratory practices and choice of the appropriate collection tube can reduce the chance of contamination while collecting the sample.

8.2.3.3.3 Sample preparation

As with the collection of the sample, key to minimizing contamination is the use of high-purity reagents and water used for sample preparation. Dilution of whole blood, serum, or plasma is usually needed to reduce the effect of the high salt, protein content, and viscosity of these matrices; however, it is important to balance the dilution and the analytical sensitivity of the method (Bolann et al. 2007). In typical ICP-MS methods, the sample is treated with a substance to break down (e.g. oxidize) the organic matrix; nitric acid (HNO_3) has been frequently used for this purpose (Matusiewicz 2009).

8.2.3.3.4 Choice of Sample Matrices

As described in earlier sections, evaluation of metal ion concentrations is often used as a surrogate of the status of the metal implant. However, no consensus has emerged regarding what kind of sample is most appropriate; serum, plasma, and whole blood measurements are used in clinical practice. While some investigations prefer the measurement of serum levels (Cornelis et al. 1996; Malek et al. 2015), it has been suggested that whole blood Co and Cr levels are a more accurate reflection of systemic exposure (Daniel et al. 2007; Hart et al. 2011). Whole blood has been recommended by the UK MHRA and FDA (Administration ; Hart et al. 2011; Agency 2017).

Measurements of paired samples drawn at the same time but processed as different sample matrices suggest that serum, plasma, and whole blood concentrations cannot be used interchangeably for testing chromium and cobalt ions. Concentrations of chromium and cobalt are significantly different between whole blood and serum (Daniel et al. 2007), and between whole blood, serum, and plasma (Malek et al. 2015; Khan et al. 2016). Another group did not find a significant difference between Co concentrations in EDTA plasma and serum (Newton et al. 2012). Bland-Altman analyses of the relationship between plasma and serum for both Cr and Co showed that the relationship between the two matrices does not consistently indicate systemic bias, suggesting that it would be inappropriate to utilize a conversion factor between the matrices (Daniel et al. 2007; Malek et al. 2015).

8.2.3.4 ***Reliability of metal ion testing***

There is limited information available regarding how well measurements of metal ions in clinical samples agree within- and between-laboratories. A comparison between the results from two laboratories (Rahme et al. 2014) found the average concentrations of Cr and Co in whole blood in the first laboratory was significantly higher than in a second laboratory. However, there were differences between instrumentation and sample preparation prior to testing to complicate the analysis. The findings in this study and in another (Saini et al. 2019) underscore that small differences in laboratories' protocols may lead to significant differences in test results. The authors emphasized that, whenever possible, patient test samples should be tested in the same laboratory to avoid the risk of misinterpreting inter-laboratory variations.

The ability of a laboratory to reliably repeat a sample value (i.e., within-laboratory value agreement) has been evaluated in a few studies. (Barry, Lavigne, and Vendittoli 2013) assessed the reliability of Cr, Co, and Ti measurements using high-resolution (HR) ICP-MS by testing sets of paired samples from 78 patients undergoing total hip MoM arthroplasty. They found the mean concentrations from the first tube were significantly higher than the mean concentrations of the second tube. They were unable to identify why there were significantly different measurements of metal ions obtained from two blood samples that were collected from the same patient at the same time and treated the same way. However, many of the samples were at or close to the limits of detection where the method may have a high imprecision.

In contrast to these studies of clinical samples, ICP-MS and related methods themselves have been shown to be reproducible within individual laboratories. For example, (Pei et al. 2012; Choi et al. 2015) have demonstrated high reproducibility and repeatability with their octupole reaction system (ORS) ICP-MS methods, with their imprecision below 6% CV in developing their analytical methodologies. Information regarding the test performance characterization data (e.g., precision, reproducibility and

accuracy) for the methodologies used in clinical laboratories that evaluate patient samples is not available to determine whether these analytical methods are sufficient.

8.2.4 Description of Lymphocyte Transformation Test (LTT)

Lymphocyte transformation tests (LTT) are whole blood-based tests that measure the *in vitro* reactivity of lymphocytes in response to antigens. LTT tests have been used since at least 1970 (Everness et al. 1990).

This technique evaluates the adaptive, T-lymphocyte-based, type IV hypersensitivity response to metals with proposed antigenic properties. Lymphocytes and other mononuclear cells obtained from a blood draw are cultured *in vitro* for several days in the presence of the metal ion such as Ni (as a potential allergen/antigen) and a radioactive tracer (often ^{3}H-thymidine incorporation into the cell's DNA). The amount of radioactivity incorporated in to the cells reflects their proliferation, a marker of cellular activity. This is usually expressed as a Stimulation Index (SI), the difference between the amount of radioactivity incorporated by cells cultured with the metal and the amount of radioactivity incorporated by cells cultured without metal (i.e., the negative control). The test always includes a positive control, usually a mitogen – a substance that non-specifically activates lymphocytes (e.g. phytohemagglutinin, PHA) (Hallab et al. 2010b).

The use of LTT is not without its challenges. Some technical challenges associated with this testing are related to the samples used. Results can be affected by blood sample stability, cell density, and the presence of low numbers macrophages in a sample. Further the results of LTT are dependent on the selection of the form of metal and metal concentration to be assessed as changes to these inputs can alter the results obtained. Separation techniques can also differ from lab to lab which can lead to concerns regarding reproducibility of LTT results.

In addition to the technical challenges discussed, there is a lack of consensus on the numerical value that must be achieved to be considered a positive SI. Various researchers define their cut-off of a positive reaction as ≥2 SI (Hallab et al. 2010b); ≥3 SI (Valentine-Thon and Schiwara 2003), or ≥ 5 SI (Pacheco et al. 2013). Finding the appropriate cut-off for the LTT for specific metals is critical for finding the right balance between false positive and false negative results and therefore a maximized clinical utility. For example, Pacheco et al. took into account that nickel can cause high immunostimulatory reactions ((Cederbrant et al. 2003; Hallab et al. 2010b) and set their positive threshold at 5.7 SI, compared with other published cutoffs of 2 or 3 SI, in order to reduce the number of false-positives.

8.2.4.1 *LTT Reproducibility*

There have been very few studies in the last 20 years that evaluate the analytical performance (e.g., precision/reproducibility/concordance etc.) of LTT tests for metal hypersensitivity. One such study evaluated the reproducibility and intra- and inter-assay variability by testing a panel of metals in a modified LTT test (i.e., LTT-MELISA test) using samples from patients with clinical symptoms suspicious of a type IV metal allergy (Valentine-Thon and Schiwara 2003). Reproducibility was tested in three ways: between-technicians, between-days, and concordance.

The actual SI values were different between the duplicates between two technicians and between the duplicates prepared by each technician; in one example of a patient positive for nickel reactions, Technician 1's positive duplicate results were 4.3 SI and 19.7 SI and Technician 2's positive duplicates

were 3.3 SI and 11.4 SI; the authors commented that the qualitative result (positive or negative) was concordant between all metals and patients.

Day-to-day variation was tested using a patient reproducibly positive for inorganic mercury tested on five different days in two- to four- week intervals. The mean SI was 34.2 ± 11.2. Because the patient was strongly positive, the variability between the days did not affect the test result.

A concordance determination of the total 196 metal tests were performed in duplicate on identical days by the same or different technicians found a concordance rate of 94%. In 11 of the 12 discordant replicates results, the positive replicate was a low SI. The reproducibility rate was 94% using a cut-off of SI = 3 or 99% using a cut-off of SI = 5.

The study also demonstrated a dose response for lymphocyte concentration; using patient samples patch-test positive for nickel, metal-specific reactivity (i.e., SI) rapidly decreased as the cell concentration; the non-specific mitogenic reactivity however was not affected by cell concentration until it was very low. Decreases in metal concentration in the cell culture similarly decreased the reactivity.

8.2.4.2 *Advantages and disadvantages of LTTs*

Under optimal conditions, LTT can identify adaptive response to a metal implant. This however does not mean there are not also several concerns associated with the use of LTT. One of the most significant regarding the identification of adverse patient responses to metal implants is that LTTs would only be able indicate those that are caused by adaptive immunity and as these responses are not limited to adaptive immunity, LTT testing alone cannot fully address the clinical need. Further, because LTTs are lab-based tests, they are not widely available for clinical use, lack standardization, and results are subject to inter-laboratory variability. In addition, the LTT is also sensitive to sample handling and may produce false negative results if the test is not transported and processed in a timely manner. Due to rapid T cell decay, even short delays can lead to false negative results (Schalock et al. 2012).

8.2.4.3 *Regulatory aspects of LTTs*

Currently, there are no LTT assays indicated for evaluating metal-induced type IV hypersensitivity reactions that are cleared or approved by the FDA. However, several clinical laboratories offer LTT tests for metal hypersensitivity as laboratory developed tests (LDTs), i.e., a diagnostic test that is manufactured by and used within a single laboratory.

8.2.4.4 *Testing Recommendations by Clinical Societies*

Similar to patch testing, routine preimplantation LTT testing is not currently recommended by clinicians (Schalock et al. 2016). Special case uses of LTT have been suggested such as those in which there is strong clinical suspicion for metal allergy however the patient had a negative patch test (Schalock et al. 2016). For example, a study conducted by Muller and Valentine-Thon found that 21 out of 56 patients with titanium alloy implants, systemic symptoms of adverse implant response, and negative skin patch testing, had positive LTT to metals. When those patients had their implants removed and replaced with non-titanium devices, they experienced significant clinical improvement (Müller and Valentine-Thon 2007). It should also be noted that 54 out of the 56, including those that had ambiguous or negative LTT results, demonstrated marked resolution of symptoms following the change to a non-titanium implant (Müller and Valentine-Thon 2007).

8.2.4.5 *Use with other evaluations*

The relationship between patch testing or imaging results and LTT results regarding implant-related metal reactivity has been somewhat contradictory. Some authors have suggested that LTT may be useful for further evaluation or confirmation in challenging cases (Teo and Schalock 2017); (Hallab et al. 2010b); (Schalock et al. 2012) while others have suggested that LTT should be preferred over patch testing (Carossino et al. 2016).

Effort has also been invested in analyzing the relationships between a positive LTT for metal, the histopathology from the revision surgery, and pre-revision and post-revision clinical and functional outcomes. Yang et al. (2019) conducted a retrospective review of 27 well-fixed aseptic TKRs revised due to persistent pain and suspected metal allergy. The authors found that based on analysis of the aforementioned parameters, positive LTT results alone were insufficient to diagnose TKA failure due to an immune reaction (Yang et al. 2019).

8.2.5 Diagnostic and screening tools summary

Good diagnostic or screening tools to evaluate the full spectrum of a patient's responses to his or her metal implant are currently lacking. It is unclear which biomarkers can reliably predict a potential pathological response to the implants. There are a limited number of ways to predict or diagnose the unexpected manifestations of metal reactivity. There are a few diagnostic tests that evaluate the response but there is no clear consensus of how these tests should be used in the clinical setting.

These gaps highlight the need for new, clinically useful diagnostic and prognostic tests for determining the likelihood of an implant-induced pathological response pre-implantation and adequately evaluating the entire scope of possible responses post-implantation.

8.3 Imaging Techniques Used to Evaluate Metal Implants

A variety of techniques are used to evaluate what is happening in, or around, an implant. Each technique has its own strengths and weaknesses. Histology requires samples of tissue removed from patient, whether obtained during an implant revision or during a biopsy to determine the cause of a patient's symptom(s), while the imaging techniques (i.e., MRI, US, and CT) discussed below do not require invasive approaches. All imaging techniques described below require a high level of technical skill to perform and interpret the findings and are subject to imprecision.

8.3.1 Histology

Histology examines very thin tissue slices, called sections, from a piece of tissue with a microscope and special dyes or molecules to determine what kind of cells and structures are present in the section. The tissue(s) and their cellular structure are preserved using chemical fixatives or by freezing rapidly. They are then embedded in a hard medium (e.g., paraffin wax, etc.) to allow microtome cut tissues sections (typically between 5-15 µm thick). Special dyes/stains are then used to enhance or contrast the general structure of the tissue, including the common hematoxylin and eosin (H&E stain), or to highlight specific structures such as fibrotic tissue (Masson trichrome) or specific kinds of cells like macrophages or T cells (enzyme-labeled antibodies).

Histology techniques have been used to elucidate the immunological processes around implanted devices containing metal. To some degree, the way pathologists have categorized the responses seen in tissues from explanted implants have become the way we describe the responses to the implant (e.g.,

ALVAL and ALTR). While several other sections discuss the immunological and mechanical processes elucidated by histopathology, this section discusses some of the approaches pathologists have standardized and used to quantify the responses viewed during microscopic analysis.

8.3.1.1 *ALVAL histology evaluation methods*

Early reports from retrieval studies focused on the lymphocyte infiltrates and necrosis seen in tissue around explanted implants. Campbell et al. (2010) developed a ten-point scale to define the tissue features around/in pseudotumor periprosthetic tissue reactions surrounding metal-on-metal hip replacements, the lymphocytic infiltrate (given a maximum of four points in a total score of ten while macrophage infiltration is given a lower score) and necrosis (scored twice in the sections for synovial lining and tissue organization, up to three points each) (Campbell et al. 2010). To determine the reproducibility between the scoring, the two experienced readers reviewed the ALVAL cases on two separate occasions and the kappa coefficient for interobserver variability showed a good correlation between the two observers of 0.71 and between the two separate measurements of each observer of 0.68, a good correlation.

Noting substantial necrosis and a heavy macrophage infiltrate in most periprosthetic tissues, Grammatopoulos et al. (2013) added components to the Campbell scale to assess the extent of tissue necrosis and measure of the inflammatory cell (macrophages, lymphocytes, plasma cells, eosinophils). It is referred to as the modified Oxford-ALVAL scale (Grammatopoulos et al. 2013). In their study, all cases were scored independently by two reviewers, finding repeatability testing demonstrated highly significant intra-observer ($k = 0.86$, $p < 0.001$) and interobserver ($k = 0.74$, $p < 0.001$) correlations.

There is surprisingly little information available about independent validation of these scales in the literature. Smeekes et al. compared the interobserver reliability of these scoring methods using three experienced pathologist's independent evaluation of periprosthetic tissue of 37 total hip revisions of failed MoM THA (Smeekes et al. 2017). The Campbell score showed an intraclass correlation (ICC) of 0.38 (fair: 95% CI, 0.18–0.58) for the sum score of all features; the modified Oxford ALVAL score ICC was 0.50 (moderate: 95% CI, 0.31–0.68). The finding of low ICC values (fair to poor) for the individual parameters between the score systems underline the low reproducibility of these morphologic findings and suggest study results using these scales should be interpreted carefully.

8.3.1.2 *ALTR histology classification evaluation methods*

In contrast to the ALVAL scales described above, recent approaches have noted that lymphocyte rich infiltrate with significant necrosis represents only a sub set of these cases. In an extensive histological analysis of 285 hip retrievals, Ricciardi et al. divided their findings into four main histological patterns :

1) macrophage predominant with absent or minimal lymphocytic response
2) mixed lymphocytic and macrophagic with or without features of associated with hypersensitivity/allergy or response to particle toxicity (eosinophils/mast cells and/or lymphocytic germinal centers)
3) granulomatous pattern, predominant or associated with the mixed inflammatory pattern and
4) predominantly lymphocytic pattern with absence of macrophagic component.

Those patients that met the criteria for one of the identified patterns were more likely to have implant failure and the macrophagic predominant pattern was more common in implants with MoM bearing surfaces. They noted the patterns are related to different implant materials and duration. Their

histological grading system included: components qualitatively describing aspects of synovial structure (e.g., present or absent); semi-quantitative evaluation of the macrophages and lymphocytes; qualitative evaluation of other cellular components; presence or absent of particles in the macrophages; and bone and bone marrow involvement as described in Perino et al. (2014) (Perino et al. 2014). Recently, an algorithm to help evaluate particles seen in histological examination was extensively reviewed and expanded (Perino et al. 2018). Particles are divided into implant wear particles and non-implant related wear particles; and characterized by size, shape, and color under a light microscopy (polarized light when necessary), and with histochemical stains when necessary. To date, these approaches have described defined scales or an assessment of reliability of inter- and intra- readers.

8.3.2 Imaging Methodologies

There has been considerable recent interest in evaluating the tissue surrounding an implant in situ using different imaging modalities such as MRI and ultrasound (US). All of these have the significant advantage of evaluating the implant and surrounding tissue in a non-invasive manner, however each has specific strengths and weaknesses.

8.3.2.1 *MRI techniques for visualizing metal implants*

Magnetic resonance imaging is another option for the assessment of adverse events with metal implants. MRI has been used because it provides excellent visualization of peri-prosthetic soft tissues and can be used to identify ARMD. Possible disadvantages of the use of this technology is that is expensive and has the potential to miss small pseudotumors or joint effusions close to the implant even with optimized imaging protocols.

Conventional MRI sequences have not produced adequate images around metal implants, however, specialized metal artifact reduction sequences (MARS) reduce the artifacts generated by metal in the adjacent tissues. The term MARS is a general term and there are several dedicated sequences and options specifically developed to reduce metal artifacts (e.g., VAT, SEMAC, and MAVRIC), reviewed recently in Talbot and Weinberg (2016) and Jungmann et al. (2017) (Talbot and Weinberg 2016); (Jungmann et al. 2017).

8.3.2.1.1 Grading systems

Anderson et al. developed an MRI grading system to evaluate the severity of ALVAL or soft tissue changes associated with MoM THA (2011) using a retrospective cohort of 73 hips, and three readers (two experienced, one less experienced) (Anderson et al. 2011). A letter grade was assigned for the extent of disease, ranging from normal (A), infection (B), and MoM disease (C) with subgrades to describe the severity of the MoM disease with C3 the most severe disease. Mild MoM disease, C1, was described as a small (< 5 cm maximum diameter) soft tissue mass or fluid-filled cavity around the prosthetic; severe MoM disease, C3, was described as any one of the following: a fluid-filled cavity extending through deep fascia; a tendon avulsion; intermediate T1W soft tissue cortical or marrow signal; or fracture. Sixty-five percent (65%) of all observations showed there was some level of soft-tissue pathology. Inter-variability between the readers was determined; the weighted kappa correlation for the two more experienced musculoskeletal radiologists was =0.78 (95% confidence intervals: 0.68–0.88). When the musculoskeletal radiologist with least experience of reporting MoM adverse effects was compared with the more experienced two observers the kappa correlation coefficients were =0.69 (95% confidence intervals: 0.57–0.80) and =0.66 (95% confidence intervals: 0.54–0.78), suggesting good

agreement between the three readers. They reported they had limited agreement between the readers in cases evaluated as grades B and C1 and suggested that the scale was best used to differentiate between normal post-operative appearances to moderate or severe disease and comment "(w)hile the grading system is reliable this does not mean that it is an accurate measure of disease." Other MRI grading systems of pseudotumors are reported in the literature , describing the walls (e.g., thin or thick); the contents (e.g., fluid or solid); and size or shape (Hauptfleisch et al. 2012; Matthies et al. 2012). However, the authors did not evaluate inter- or intra-variability in their original papers.

8.3.2.1.2 Comparison of pseudotumor grading systems with MRI

Two studies have compared three MRI-MARS pseudotumor grading systems. As noted in Anderson (2011), Hauptfleisch (2012), and Matthies (2011) (Anderson et al. 2011; Hauptfleisch et al. 2012; Matthies et al. 2012). In a cohort of 49 hips (van der Weegen et al. Skeletal Radiology 2014), two experienced independent readers read the scans; for intra-observer reliability the cases were read again two months later (van der Weegen et al. 2014). Detection of pseudotumors in the hips was between 41% to 47% of the 49 hips evaluated, depending on the grading system and the reader. discussion: Interobserver reliability on whether a pseudotumor was present or not was 0.92 ($p < 0.001$) with the Anderson system; 0.84 ($p < 0.001$) with the Matthies system; and 0.79 ($p < 0.001$) with the Hauptfleisch system. In this study, intra-observer reliability for grading pseudotumor severity on MARS-MRI ranged from poor to good, dependent on observer and grading system used. Interobserver reliability scored best with the Anderson system. Intra-observer reliability on grading pseudotumor severity with the Anderson, Matthies, and Hauptfleisch grading system scored 0.47, 0.10, and 0.35 (observer 1), and 0.75, 0.38, and 0.42 (observer 2), respectively. Interobserver reliability scores for pseudotumor severity were 0.58, 0.23, and 0.34, respectively. Importantly, the authors calculated the intra- and interobserver reliability on grading pseudotumor severity was calculated by excluding cases with no pseudotumor; thus, the findings of this study may not be comparable to other evaluations of reliability.

In a larger study, of scans of 240 hips, Smeekes et al. (2018) compared the three grading systems to determine the interobserver reliability of the grading systems. Two readers identified pseudotumors in 45% and 40% scans, respectively ((Smeekes et al. 2018)). Interobserver reliability on whether a pseudotumor was present or not was 0.56 ($p = <0.001$); however, there was limited agreement between the individual grading scores; for example, there was only 17% complete agreement between reader 1 and reader 2 for Anderson C1 scores, 68% for Anderson C2, and 6% for Anderson C3. Between the grading scales, the kappa values of the Anderson, Hauptfleisch and Matthies grading system scores were 0.43, 0.44, and 0.49 respectively, suggesting moderate agreement (Anderson et al. 2011; Hauptfleisch et al. 2012; Matthies et al. 2012).

8.3.2.2 ***Ultrasound (US) techniques for visualizing metal implants***

There are also several benefits to assessing metal implants using ultrasound. Specifically, with ultrasound there is no ionizing radiation, reduced expense, absence of metal artifacts introduced by implants in the imaging and no contraindications for patients with some cardiac pacemakers and ferromagnetic surgical materials. When utilizing US for visualizing implants, clinicians should also consider that this approach may be operator-dependent and that it may be difficult to access deep tissues in obese patients. When compared to US, MRI may provide superior imaging results in cases where there is abnormal soft-tissue and has the ability to assess the implant in three dimensions.

8.3.2.2.1 Classification system

Classification systems for evaluating the status of the tissues around metal implants do not seem to have been as rigorously assessed or widely adopted as with some of the MARS-MRI scales described earlier.

Nishii et al. (2012) described four qualitative patterns on US of the hip: normal; "joint-expansion pattern" with marked hypoechoic space of 4 mm or more, between the anterior capsule and the anterior surface of the femoral component; "cystic pattern," with irregularly shaped hypoechoic lesions extending anterior to the femoral component; and mass pattern" with a large mass "extending anterior to the femoral component (Nishii et al. 2012). While 88 hips were evaluated, only 19 hips presented the three non-normal patterns. The limited size of the study however, prevented the validation of the abnormal patterns observed and did not determine the inter- or intra-reader variability.

Siddiqui 2013 developed a systematic methodology to evaluate pseudotumors and muscle atrophy in periprosthetic tissues of patients around MoM hips by describing how they perform ultrasound examinations and by describing the finding using scales used for MARS MRI adapted for ultrasound use. They did not evaluate the inter- or intra-reader variability (Siddiqui et al. 2013). They used their ultrasound scale in a study described below.

8.3.2.2.2 Comparison of Ultrasound Imaging and MARS-MRI in detecting adverse effects and utility for screening

Garbuz et al. performed a prospective evaluation of 40 asymptomatic patients who received a large-head MoM THA to determine if US or MRI was superior in detecting pseudotumors. Patients received an US and an MRI on the same visit (Garbuz et al. 2014). 'Truth' was defined as both modalities detected the presence of a pseudotumor. Three readers for both MRI and US images; one sonographer, experienced in musculoskeletal imaging performed the ultrasound examinations. The study did not histologically confirm the presence of pseudotumor(s) but rather a concordance evaluation than a true assessment of diagnostic accuracy of the imaging tools. They found concordance between the two modalities in 93% (37 of 40) of patients with US demonstrating a sensitivity of 100% and specificity of 96%, whereas MRI had a sensitivity of 92% and specificity of 100%. No intra- or interobserver reliability testing was done (Garbuz et al. 2014).

In another study, Nishii et al. (2014) compared the agreement of ultrasound screening for ALTR in 131 hips of 105 patients who received both ultrasound and MRI examinations after hip arthroplasty with MoM or highly cross-linked polyethylene (HXLPE) bearings. Between the ultrasound and MRI findings, there was substantial agreement for the detection of abnormal lesions in both the MoM group (kappa values = 0.67) and the HXLPE group (κ values = 0.66) (Nishii et al. 2014). Using the MRI findings as a reference, the sensitivity, specificity and accuracy for the detection of abnormal lesions by ultrasound examinations were 74%, 92% and 84%, respectively, in the MoM group, and 90%, 83%, and 85%, respectively, in the HXLPE group. US failed to detect ALTR in nine hips (seven in the MoM group and two hips in the HXLPE group). Conversely, the ultrasound examinations detected ALTR in 11 hips (three in the MoM group and eight hips in the HXLPE group) that was not shown with MRI. There were no significant differences in detecting abnormal lesions by ultrasound between the two groups. This study did not evaluate the severity of ALTR or its use in deciding whether revision surgery is warranted. While suggesting the diagnostic potential (i.e., the sensitivity and specificity of ALTR) of ultrasound, this study did not evaluate asymptomatic patients as would a screening program.

Siddiqui et al. compared the diagnostic accuracy and characteristics of US using MARS MRI as a reference for the detection of pseudotumors and muscle atrophy in painful MoM hip arthroplasty (Siddiqui et al. 2014). This study found US was inferior to MARS-MRI for the detection of pseudotumors and muscle atrophy (53% US to 68% MRI) but US was superior to MARS MRI in detecting joint effusion (10 cases by US but no cases by MRI). The Siddiqui paper utilized grading approaches and definitions first outlined in their 2013 paper for the US and the Hart et al. (2012) study evaluating pseudotumors in well-functioning MoM hips with MARS-MRI (Siddiqui et al. 2013); (Hart et al. 2011). It should be noted that the inclusion of all pseudotumors may have complicated the findings.

8.3.2.2.3 Utility of longitudinal ultrasound in adverse event detection

The emergence of ultrasound as a diagnostic tool in identifying the cause of a patient's adverse reaction has encouraged studies on the utility of repeat ultrasound imaging as a component of follow-up care in metal-on-metal hip arthroplasty patients (Matharu et al. 2016). Almousa et al. described a study of 20 asymptomatic patients with pseudotumors were followed. Initial assessment was on mean at 25.8 months (range, 21–31 months) after the surgery; changes in pseudotumors and fluid collections size and nature, and serum ion levels were determined. On a follow-up ultrasound (at a mean of 66 months from the surgery), three of six large femoral head MoM THA group had what was defined as clinically important increases in volume, one patient's pseudotumor did not change much, and two patients' small pseudotumors disappeared (Almousa et al. 2013a).

Other studies have supported these findings. Garbuz et al. reported that they found substantial increases in lesion size in only two of eight patients followed over an average of seven months (Garbuz et al. 2014). Matharu et al. (Matharu et al. 2016), found 27% (n=13) of MoM THAs in their cohort of 96 hips had an increase in grade between scans; 67% (n =32) had no change in grade; and 6% (n = 3) had a reduction in grade over the mean time interval of 1.1. years (range, 0.2 – 3.3 years). These studies suggest that repeat US imaging in patients with MoM hips may be useful for identifying development and progression of lesions, but the definition of progression should be carefully defined.

Kwon et al. (2016) used US to prospectively follow the sensitivity and specificity of the ultrasound for detecting ALTR in relation to MARS MRI during two longitudinal follow-up scans of 35 MoM patients (42 hips) (Kwon et al. 2016). The authors determined the extent to which agreement existed between ultrasound and MARS MRI in ALTR grade, size, and size change was determined. High agreement (k = 0.85 was found between U/S and MARS MRI in detecting any change in ALTR size or grade. From the initial evaluation and subsequent follow-up at 14 months (mean, range 13 – 18 months), ultrasound was found to have had a sensitivity of 81% and 86% and a specificity of 92% and 88%, respectively, with MARS-MRI as the gold standard. Ultrasound was able to detect the "change" in the lesions size with ~0.3 cm^2 average bias from the MARS MRI at the follow-up evaluations with higher agreement (k = 0.85) with MARS MRI compared to the initial evaluation in detecting any "change" in ALTR size or grade. The authors conclude that ultrasound can demonstrate comparable diagnostic accuracy with MARS MRI in detecting the presence of ALTR during longitudinal evaluation of MoM patients.

9 CHALLENGES

Gaps exist in both our knowledge base and the available tools that are necessary to understand and assess biological responses to metal implants in clinical and regulatory contexts. One of our fundamental challenges is that the mechanisms underlying the biological responses to metal implants are not fully understood. Because of this, it is difficult to distinguish between the device- and patient-related factors in addressing safety and effectiveness concerns. Overcoming this challenge is necessary to help manufacturers design appropriate pre-market studies and develop appropriate acceptance criteria. Further, there are only a few validated tests that assess adverse responses to metal implants and currently there is no clear evidence or agreement on how these tests should be used for clinical and regulatory decisions.

Another fundamental challenge is that scientists, clinicians, and regulators do not necessarily use a common set of terms and definitions across respective fields. For example, the term 'metal allergy' is often used when discussing several different immunological responses to a foreign substance, many of which may have minimal or no involvement of true allergic reactions.

Of all the challenges concerning biological responses to metal implants, perhaps the most important is being able to detect subtle but consequential biological responses that may indicate a potential safety concern during CDRH post-market device monitoring.

9.1 INTRODUCTION

The FDA and the scientific and healthcare community will need to consider and address several individual and related challenges pertaining to adverse effects associated with metal implants. The pathological mechanisms of metal reactivity are not well established and the interplay between

different physiological and immunological processes remains to be elucidated. It is unclear why some patients not only have unexpected clinical responses to metal implants but also why a spectrum of pathological responses (from local effects to multi-systemic reactions) can be observed. Fundamental scientific questions in need of further evaluation include the extent and mechanism by which certain metals and/or alloys may cause or contribute to immunologically-related events; factors or scenarios which may convey a higher likelihood of an unexpected or exaggerated immunological response to a metal-containing implant for an individual; and, diagnostic methods or other mitigation strategies which may predict or reduce the likelihood or severity of a patient's response to a metal-containing implant.

9.2 Common Terminology

Before these challenges can be addressed, a common set of definitions and terminology is preferable to understand adverse responses of metal implants. Scientists, clinicians, and regulators do not necessarily use a common set of terms and definitions across respective fields. For example, as the most frequently cited toxicological effects of metals, the definitions of 'hypersensitivity' and 'allergy' are subject to controversy mainly due to unreliable diagnostic tests. Moreover, published evidence for implant failure due to true allergy is lacking and type IV hypersensitivity is not clinical evidence-based.

9.3 In Vivo Corrosion

The lack of available data to correlate *in vitro* and in vivo corrosion and metal ion release represents one of the main challenges in understanding the biological responses to metal implants and for future product design considerations. In vivo corrosion studies, while limited, have been reported; however, existing corrosion testing methods do not adequately simulate *in vivo* conditions where cells, proteins, mechanical loading, and other factors can impact ion release. For instance, in cardiovascular and orthopedic devices, corrosion by-products are limited to measuring concentration of metal ions in serum and urine. In active implants, such as platinum electrodes and cardiac devices, SEM has been utilized to observe electrode pitting and platinum release. Immersion testing for general corrosion and metal ion release in passive and active implants *in vitro* is typically performed to measure metal ion release from the metallic device in physiologically relevant media. While metal ion testing has been widely reported in literature it is important to note that a variety of factors must be considered when interpreting the results. One critical factor is that testing does not reproduce the in vivo environment, thus, how the data translates clinically is unclear.

There are also three FDA recognized ASTM standards to test for local, galvanic, and fretting corrosion *in vitro*. ASTM F2129 is an accelerated nonclinical method to assess pitting corrosion potential of medical devices by quantifying the voltage required to induce pitting on the device surface. While there is no general standard test method to evaluate fretting of medical devices, ASTM F1875, which is specific to orthopedic devices, suggests evaluating device damage from fretting and determining if design changes impact fretting susceptibility. Galvanic corrosion testing for devices that contain different alloys in direct contact follows ASTM F3044. Even with these recognized consensus standards, establishing universal acceptance criteria for *in vitro* testing remains a challenge due to the limited in vivo data available. Therefore, understanding patient risk associated with corrosion from metallic implants presents a significant knowledge gap.

Because metal corrosion testing is typically done under idealized conditions, which enables comparisons between devices, it is still unclear how *in vitro* engineering performance correlates to the corrosion

behavior with *in vivo* implantation. Although qualitative consistency between engineering testing and behavior inside the body between devices exists, quantification of these relationships using computer models, engineering testing, tissue and *ex vivo* body fluid evaluations, testing within the human body (e.g., imaging), and/or clinical studies is important for corrosion prediction within individual patients.

9.4 Pre-market Biocompatibility Assessment

CDRH's 2016 Biocompatibility Guidance illustrates important information that can assist in the evaluation of probable adverse biological responses from device components in contact with the body. While there are a host of FDA recognized biocompatibility standards, questions remain regarding how to successfully evaluate the safety and effectiveness of metal implants outside of clinical studies. This is primarily due to insufficient evidence from nonclinical models that may adequately address biological responses from wear debris or determine consequences from long-term exposure to implants in vivo. For instance, animal studies for biocompatibility assessments do not investigate tissue response to mechanical failures even though differences in anatomy and mechanism between animals and humans are recognized. This is further limited by the lack of quantitative correlation between *in vitro* and in vivo studies of metal ion release and corrosion.

Recommended biocompatibility endpoints that may be affected by the metallic components of the device could be assessed using various approaches. Hypersensitivity and allergic reactions, the most common immunotoxicological effects of metals, are typically evaluated with assays such as the Buehler Test (in animals) and the human repeat insult patch test (HRIPT). While assays to detect delayed Type IV hypersensitivity exist, whether patients should be screened for metal hypersensitivity prior to implantation remains subject to debate and an important issue to resolve. Moreover, recommended standards to assess the potential for adverse systemic effects from the release of chemical compounds from a device have their drawbacks. For example, ISO 10993-11 does not account for the fact that target organ toxicities can occur without changes in body weight and "clinical observations." Additionally, chemical characterization/risk assessment using ISO 10993-1 and the CDRH Biocompatibility Guidance can only be used if toxicity data are available for particles with the exact physical-chemical properties as those released from the device. Furthermore, sensitization or hypersensitivity is not used as an endpoint for chemical characterization/risk assessment. Limitations in biocompatibility assessments thus present unique challenges in premarket evaluation of the device.

9.5 Cellular and Molecular Science

Current investigations suggest that the specific local tissue responses to metal implants are dependent on several factors: the device, the biomaterial, peri-implant tissue type, as well as patient-related characteristics. Several existing standards provide guidance to evaluate different aspects of the implant-related response such as pyrogenicity, immunotoxicity, or cytotoxicity. These and other biological endpoint-specific testing standards, are used together to constitute the basis for assessing implant-related effects. However, none of the currently available standards encompasses overall testing that evaluates inflammation (not limited to hypersensitivity and allergy) as the main underlying pathophysiological process and sufficiently assesses the implant-related inflammatory responses. Because immune and inflammatory responses are coordinated, understanding of the role of each of these factors on implant reactions is needed. Significant gaps remain in understanding the role of both innate and adaptive, acquired immunity in normal responses to implant, implant failure, and other

adverse events. While allergies to nickel, cobalt, and chromium ions are common, causative relationships between true allergic reactions and adverse outcomes from metal implants remains to be demonstrated.

Further research is needed to understand the underlying cellular and molecular mechanisms which can detect signals predictive of metal implant failure, as maladaptive responses that lead to failure or adverse events may appear like normal responses. Cellular, tissue, and timing contexts of responses that may distinguish maladaptive from normal responses is also needed.

9.6 CLINICAL

The clinical response to metal implants is complicated and no simple explanation for the wide variety of suggested responses is available. These contexts are highly diverse: patient history, genetic background, variations in environment and lifestyle, and underlying disease and comorbidity. Despite commonly used terms such as “metal allergy” or “metal hypersensitivity”, current published evidence suggests that allergic mechanisms alone do not explain most responses to metal implants. Further, there is a lack of standard terminology, reliable study endpoints, and testing methods to address the involvement of both types of immunity (innate and adaptive) and to encompass the entire spectrum of inflammation-related biological responses associated with metal implants.

Although local and systemic responses are known to manifest in patients with metal implants it remains unclear if metal “allergy” is a cause or consequence of device failure. For example, in terms of MoM hips, while evaluation of metal ion levels and imaging around the metallic implant are recommended for symptomatic patients, reports of elevated metal ions with minimal symptoms and normal radiographs suggests a lack of correlation with adverse reactions to metal debris (ARMD) development. Additionally, type IV hypersensitivity may not drive pseudotumor development since significant differences may not be observed in lymphocyte reactivity to cobalt (Co), chromium (Cr), and nickel (Ni) between MoM hip resurfacing cases with and without pseudotumors. However, Co and Cr blood levels may be found to be higher in MoM macrophage-dominated hip pseudotumor cases. Although not confirmed, studies have shown that revisions with low wear have higher aseptic lymphocytic vasculitis-associated lesion (ALVAL) scores indicative of type IV hypersensitivity, while revisions with high wear have lower ALVAL scores due to macrophage response and metal debris cytotoxicity.

Harmful responses are often the result of device, biomaterial, and patient-related factors. Individual patient susceptibility likely plays an important role in the outcome, raising questions about how an implant recipient’s immune system may respond to the presence of metal in/from the device and to what degree, if any, that response may produce clinically meaningful signs, symptoms or adverse outcomes. Special populations which may be more susceptible to foreign substances have not been identified.

Additional characterization of the nature and frequency of adverse reactions to metal implants is needed. Distinguishing responses of metallic devices to different physiological conditions may promote development of proper diagnostic and prognostic tools and help better understand a patient’s adverse responses to their metallic implants.

9.7 Laboratory and Diagnostic Testing

Significant gaps exist in both our knowledgebase and the available tools that are necessary to understand and assess biological responses to metal implants. One of our fundamental challenges is that the actual mechanisms underlying the biological responses to metal implants are not fully understood. Because of this, it is difficult to distinguish between the device-and patient-related factors in addressing adverse reactions. Overcoming this challenge is necessary to help design appropriate pre-market studies and develop appropriate acceptance criteria.

Furthermore, there are only a few validated tests that assess adverse responses to metal implants. There is no clear evidence and agreement on how these tests should be used for clinical and regulatory decisions. While some aspects of inflammation are addressed in several of FDA's currently recognized standards, none of the currently existing standards provides an all-inclusive guidance for comprehensive assessment of the overall inflammatory response that would incorporate nonclinical and clinical testing. Lack of standardized material testing, and immunological/radiological testing also hinders our ability to adequately predict safety signals should new metals and/or materials be used in the future.

9.8 Post-market Surveillance

The main challenge in both pre- and post-market phases of regulatory review is the lack of adequate study endpoints and diagnostic and/or prognostic tools which reliably predict clinical responses. The threshold for detecting subtle but consequential biological responses which may constitute signals in our post-market surveillance systems remains to be determined. Currently, it is extremely difficult to determine whether symptoms are related to the implanted device or other causes. Predictive assessment of the proinflammatory potential and subsequent tissue remodeling remains a major challenge affecting real-world performance of implantable devices and biomaterials. Real world evidence and patient registries may be helpful in this regard.

APPENDIX A: TABLE OF ACRONYMS USED

Acronym	Meaning
AAAAI	Academy of Allergy, Asthma, and Immunology
AAGL	American Association of Gynecologic Laparoscopists
AAMI	Association for Advancement of Medical Instrumentation
ACD	Allergic Chronic Dermatitis
ACDS	American Contact Dermatitis Society
ALCL	Anaplastic Large Cell Lymphoma
ALTR	Adverse Local Tissue Reactions
ALVAL	Aseptic Lymphocytic (Lymphocyte-Dominated) Vasculitis-Associated Lesions
ANSI	American National Standards Institute (https://www.ansi.org/)
ARMD	Adverse Reaction to Metal Debris
ASIA	Autoimmune/Autoinflammatory Syndrome Induced by Adjuvants
ASTM	American Society for Testing Materials International https://www.astm.org/about/faqs.html
Au	Gold
Buehler Test	Guinea Pig Closed Patch Sensitization Test

CA	Chromosomal Aberration
CBC	Complete Blood Count
CDRH	Center for Devices and Radiological Health
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
Co	Cobalt
Cr	Chromium
Cu	Copper
DNA	Deoxyribonucleic Acid
ESCD	European Society of Contact Dermatitis
ESR	Erythrocyte Sedimentation Rate
FBR	Foreign Body Reaction
FCA	Freund's Complete Adjuvant
FDA	Food and Drug Administration
Fe	Iron
FMF	Familial Mediterranean Fever
GPMT	Guinea Pig Maximization Test
HXLPE	Highly Cross-Linked Polyethylene
IARC	International Agency for Research on Cancer
ICD	Implantable Cardioverter Defibrillators
ICSR	Individual Case Safety Report
ISO	International Organization for Standardization
ISR	In-Stent Restenosis
IUD	Intrauterine Devices
IVD	In-Vitro Diagnostic
LDT	Laboratory Developed Tests
LLNA	Local Lymph Node Assay
LTT	Lymphocyte Transformation Test
MARS	Metal Artifact Reduction Sequences
MAUDE	Manufacturer and User Facility Device Experience
MDR	Medical Device Reports
Mn	Manganese

MN	Micronucleus
Mo	Molybdenum
MOM	Metal-On-Metal
MoP	Metal-On-Polyethylene
MRI	Magnetic Resonance Imaging
Ni	Nickel
NIH	National Institutes of Health
NJR	National Joint Registry of England and Wales
OA	Osteoarthritis
OECD	Organisation for Economic Co-Operation and Development
PED	Pipeline Endovascular Device
PFO	Patent Foramen Ovale
PMMA	Polymethylmethacrylate
PTFE	Polytetrafluoroethylene
RA	Rheumatoid Arthritis
SCD	Systemic Contact Dermatitis
SEM	Self-Expandable Metallic Stents
SI	Lymphocyte Stimulation Index
SNAS	Systemic Nickel Allergy Syndrome
T-cells	T Lymphocyte Cells (Type of White Blood Cells)
THA	Total Hip Arthroplasty
Ti	Titanium
TI	Tolerable Intake
TKR	Total Knee Replacement
TLR4	Toll-Like Receptor 4
TMJ	Temporomandibular
Type IV hypersensitivity	A Delayed Hypersensitivity Reaction Mediated by T Lymphocytes (Or T-Cells)
UHMWPE	Ultra-High Molecular Weight Polyethylene
US	Ultrasound
USP	United States Pharmacopeia
TRUE	Thin-Layer Rapid Use Epicutaneous Patch Test

APPENDIX B: CURRENT LANDSCAPE OF METAL IMPLANT DEVICE TYPES CLEARED OR APPROVED BY FDA

Metal Implant Device Type	Clinical Application Areas	Duration of Implantation	Type of Metals or Alloys Used	FDA cleared/approved device submissions			Regulatory Class of Device
				2006	2016	10-year cumulative	
Bone fixation devices (plates, screws, wires, pins, rods)	Orthopedic, oral, maxillofacial, reproductive, ENT, ophthalmology	Temporary, Permanent	Ti, SS, Ni –Ti, Au, Ag, Pt-alloys	432	608	6573	Class II
Prosthesis	Orthopedic, oral, maxillofacial, Reproductive, ENT, ophthalmology	Permanent	Ti, Co-Cr alloys, SS, Au, Ag, Pt-alloys, Sn-Ag, Ni	389	390	4362	Class II/III Majority II
Soft tissue fixation devices (clips/sutures/ staples)	General and specialized surgery	Temporary, Permanent	Ti, SS, Pt, Ta, Ni-Co, Ni-Ti, Au, Pt-alloys, Co-Cr alloys	28	34	346	Class II/III Majority II
Catheters, ports, and shunts	Vasculature, GI, urology, reproductive	Temporary, Permanent	Ti, SS, Ni-Ti, Pt alloys	38	28	364	Class II/III Majority II
Stents, valves, and tubal inserts		Temporary, Permanent	Ti, SS, Ni-Ti, Al, Co-Cr-alloys, W, Pt alloys	16	26	246	Class II/III Majority II
Electrical stimulators, receivers, sensors and electromechanical devices	Neurology, cardiology, urology, ENT, endocrinology	Permanent	Ti, SS, Ag, Co-Cr-alloys, Pt-alloys, Au, Ta	5	12	101	Class II/III Majority II

ABBREVIATIONS: Ti: titanium or titanium alloy, SS: stainless steel. Ni-Ti: nitinol, Co-Cr and Co-Cr-Mo (or similar): cobalt-chromium-alloy, Ta: tantalum, Au: gold, Ag: silver, Pt and Pt-Ir (or similar): platinum-alloy, Sn-Ag: tin-silver alloy, W: tungsten

APPENDIX C: TABLE OF FDA RECOGNIZED BIOCOMPATIBILITY STANDARDS

Standard Developing Organization	*Standard Designation Number/Date*	*Title of Standard*	*Recognition* (as of September 2019)*
ISO[18]	10993-1 Fifth edition 2018-08	Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process	*See supplementary information for extent of recognition
ISO	10993-10 Third Edition 2010-08-01	Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization	Complete standard
AAMI[19] *ANSI*[20] *ISO*	10993-10:2010/(R)2014	Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization	Complete standard
ISO	10993-11 Third edition 2017-09	Biological evaluation of medical devices - Part 11: Tests for systemic toxicity	Complete standard
ISO	10993-12 Fourth edition 2012-07-01	Biological evaluation of medical devices - Part 12: Sample preparation and reference materials	*See supplementary information for extent of recognition
AAMI ANSI ISO	10993-12:2012	Biological evaluation of medical devices - Part 12: Sample preparation and reference materials	*See supplementary information for extent of recognition

[18] International Organization for Standardization (ISO)
[19] Association for the Advancement of Medical Instrumentation (AAMI)
[20] American National Standards Institute (ANSI)

ISO	10993-13 Second edition 2010-06-15	Biological evaluation of medical devices - Part 13: Identification and quantification of degradation products from polymeric medical devices	*See supplementary information for extent of recognition
AAMI ANSI ISO	10993-13:2010/(R)2014	Biological evaluation of medical devices - Part 13: Identification and quantification of degradation products from polymeric medical devices	*See supplementary information for extent of recognition
ISO	10993-14 First edition 2001-11-15	Biological evaluation of medical devices - Part 14: Identification and quantification of degradation products from ceramics	Complete standard
AAMI ANSI ISO	10993-14:2001/(R) 2011	Biological evaluation of medical devices - Part 14: Identification and quantification of degradation products form ceramics	Complete standard
ISO	10993-16 Third edition 2017-05	Biological evaluation of medical devices - Part 16: Toxicokinetic study design for degradation products and leachables	Complete standard
ISO	10993-17 First edition 2002-12-01	Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances.	*See supplementary information for extent of recognition
AAMI ANSI ISO	10993-17:2002/(R)2012	Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances	*See supplementary information for extent of recognition
ISO	10993-2 Second edition 2006-07-15	Biological Evaluation of medical devices - Part 2: Animal welfare requirements	Complete standard
AAMI ANSI ISO	10993-2:2006/(R)2014	Biological Evaluation of medical devices - Part 2: Animal welfare requirements	Complete standard
ISO	10993-3 Third edition 2014-10-1	Biological evaluation of medical devices - Part 3: Tests for genotoxicity carcinogenicity and reproductive toxicity	*See supplementary information for extent of recognition
AAMI ANSI ISO	10993-3:2014	Biological evaluation of medical devices - Part 3: Tests for genotoxicity carcinogenicity and reproductive toxicity	*See supplementary information for extent of recognition
ISO	10993-4 Third edition 2017-04	Biological evaluation of medical devices – Part 4: Selection of tests for interaction with blood	Complete standard
ISO	10993-5 Third edition 2009-06-01	Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity	Complete standard
AAMI ANSI ISO	10993-5:2009/(R)2014	Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity	Complete standard

ISO	10993-6 Third edition 2016-12-01	Biological evaluation of medical devices - Part 6: Tests for local effects after implantation	Complete standard
ISO	10993-9 Second edition 2009-12-15	Biological evaluation of medical devices - Part 9: Framework for identification and quantification of potential degradation products	*See supplementary information for extent of recognition
AAMI ANSI ISO	10993-9:2009/(R)2014	Biological evaluation of medical devices - Part 9: Framework for identification and quantification of potential degradation products	*See supplementary information for extent of recognition
ISO	14155 Second edition 2011-02-01	Clinical investigation of medical devices for human subjects - Good clinical practice [Including: Technical Corrigendum 1 (2011)]	*See supplementary information for extent of recognition
AAMI ANSI ISO	14155:2011	Clinical investigation of medical devices for human subjects - Good clinical practice	*See supplementary information for extent of recognition
USP [21]	41-NF36:2018	<87> Biological Reactivity Test, In Vitro -- Direct Contact Test	Complete standard
USP	41-NF36:2018	<87> Biological Reactivity Test, In Vitro -- Elution Test	Complete standard
USP	41-NF36:2018	<88> Biological Reactivity Tests, In Vivo	*See supplementary information for extent of recognition
USP	41-NF36:2018	<151> Pyrogen Test (USP Rabbit Test)	*See supplementary information for extent of recognition
AAMI ANSI	BE83:2006/(R)2011	Biological evaluation of medical devices - Part 18: Chemical characterization of materials	*See supplementary information for extent of recognition
ASTM [22]	E1262-88 (Reapproved 2018)	Standard Guide for Performance of the Chinese Hamster Ovary Cell/Hypoxanthine Guanine Phosphoribosyl Transferase Gene Mutation Assay	Complete standard
ASTM	F1408-97 (Reapproved 2013)	Standard Practice for Subcutaneous Screening Test for Implant Materials	Complete standard
ASTM	F1439-03 (Reapproved 2018)	Standard Guide for Performance of Lifetime Bioassay for the Tumorigenic Potential of Implant Materials	Complete standard

[21] United States Pharmacopeia (USP)
[22] American Society for Testing and Materials International (ASTM)

ASTM	F1877-16	Standard Practice for Characterization of Particles	Complete standard
ASTM	F1903-18	Standard Practice for Testing for Biological Responses to Particles In Vitro	Complete standard
ASTM	F1904-14	Standard Practice for Testing the Biological Responses to Particles In Vivo	Complete standard
ASTM	F1983-14	Standard Practice for Assessment of Compatibility of Absorbable/Resorbable Biomaterials for Implant Applications	Complete standard
ASTM	F1984-99 (Reapproved 2018)	Standard Practice for Testing for Whole Complement Activation in Serum by Solid Materials	Complete standard
ASTM	F2147-01 (Reapproved 2016)	Standard Practice for Guinea Pig: Split Adjuvant and Closed Patch Testing for Contact Allergens	Complete standard
ASTM	F2148-18	Standard Practice for Evaluation of Delayed Contact Hypersensitivity Using the Murine Local Lymph Node Assay (LLNA)	Complete standard
ASTM	F2382-18	Standard Test Method for Assessment of Circulating Blood-Contacting Medical Device Materials on Partial Thromboplastin Time (PTT)	Complete standard
ASTM	F2888-19	Standard Practice for Platelet Leukocyte Count - An In-Vitro Measure for Hemocompatibility Assessment of Cardiovascular Materials.	Complete standard
ASTM	F2901-19	Standard Guide for Selecting Tests to Evaluate Potential Neurotoxicity of Medical Devices	Complete standard
ASTM	F619-14	Standard Practice for Extraction of Medical Plastics	Complete standard
ASTM	F719-81 (Reapproved 2012)	Standard Practice for Testing Biomaterials in Rabbits for Primary Skin Irritation	Complete standard
ASTM	F720-17	Standard Practice for Testing Guinea Pigs for Contact Allergens: Guinea Pig Maximization Test	Complete standard
ASTM	F748-16	Standard Practice for Selecting Generic Biological Test Methods for Materials and Devices	*See supplementary information for extent of recognition
ASTM	F749-13	Standard Practice for Evaluating Material Extracts by Intracutaneous Injection in the Rabbit	Complete standard

ASTM	F750-87 (Reapproved 2012)	Standard Practice for Evaluating Material Extracts by Systemic Injection in the Mouse	Complete standard
ASTM	F756-17	Standard Practice for Assessment of Hemolytic Properties of Materials	Complete standard
ASTM	F763-04 (Reapproved 2016)	Standard Practice for Short-Term Screening of Implant Materials	Complete standard
ASTM	F813-07 (Reapproved 2012)	Standard Practice for Direct Contact Cell Culture Evaluation of Materials for Medical Devices	Complete standard
ASTM	F895-11 (Reapproved 2016)	Standard Test Method for Agar Diffusion Cell Culture Screening for Cytotoxicity	Complete standard
ASTM	F981-04 (Reapproved 2016)	Standard Practice for Assessment of Compatibility of Biomaterials for Surgical Implants with Respect to Effect of Materials on Muscle and Bone	Complete standard
ISO	TS 10993-19 First edition 2006-06-01	Biological evaluation of medical devices - Part 19: Physicochemical morphological and topographical characterization of materials	*See supplementary information for extent of recognition
AAMI ANSI ISO	TIR 10993-19:2006	Biological evaluation of medical devices - Part 19: Physicochemical morphological and topographical characterization of materials	*See supplementary information for extent of recognition
ISO	TS 10993-20 First edition 2006-08-01	Biological evaluation of medical devices - Part 20: Principles and methods for immunotoxicology testing of medical devices	*See supplementary information for extent of recognition
AAMI ANSI ISO	TIR 10993-20:2006	Biological evaluation of medical devices - Part 20: Principles and methods for immunotoxicology testing of medical devices	*See supplementary information for extent of recognition
ISO	TR 10993-33 First Edition 2015-03-01	Biological evaluation of medical devices - Part 33: Guidance on tests to evaluate genotoxicity - Supplement to ISO 10993-3	*See supplementary information for extent of recognition
ISO	TS 21726:2019	Biological evaluation of medical devices - Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents	Complete standard
ISO	TR 37137 First edition 2014-05-15	Cardiovascular biological evaluation of medical devices - Guidance for absorbable implants	*See supplementary information for extent of recognition

AAMI ANSI ISO	TR 37137:2014	Cardiovascular biological evaluation of medical devices - Guidance for absorbable implants	*See supplementary information for extent of recognition

*FDA Recognized Consensus Standards

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