Bridging Knowledge Gaps in PBPK through Open Science

Marc R. Gastonguay, Ph.D.
Matthew M. Riggs, Ph.D.

METRUM
RESEARCH GROUP

Contributors to Knowledge Gaps in PBPK

1 **Growth of Science (Global Knowledge Gaps)**
- Emerging information on quantitative physiology: e.g. ontogeny, expression levels
- New therapeutic modalities and targets

2 **Closed Science (Local Knowledge Gaps / Silos)**
- Currently, most published PBPK modeling results are not reproducible
- Missed opportunity to share precompetitive learnings

PBPK Knowledge Growth with Open Science

PBPK Models
Disentangled from
PBPK Software

Transparent & Reproducible
Model Specification

Quality Software & Model
Development Life Cycles

Open Provenance
of Model Parameter
Derivation

Community Engagement
in Model Verification &
Validation

PBPK KNOWLEDGE
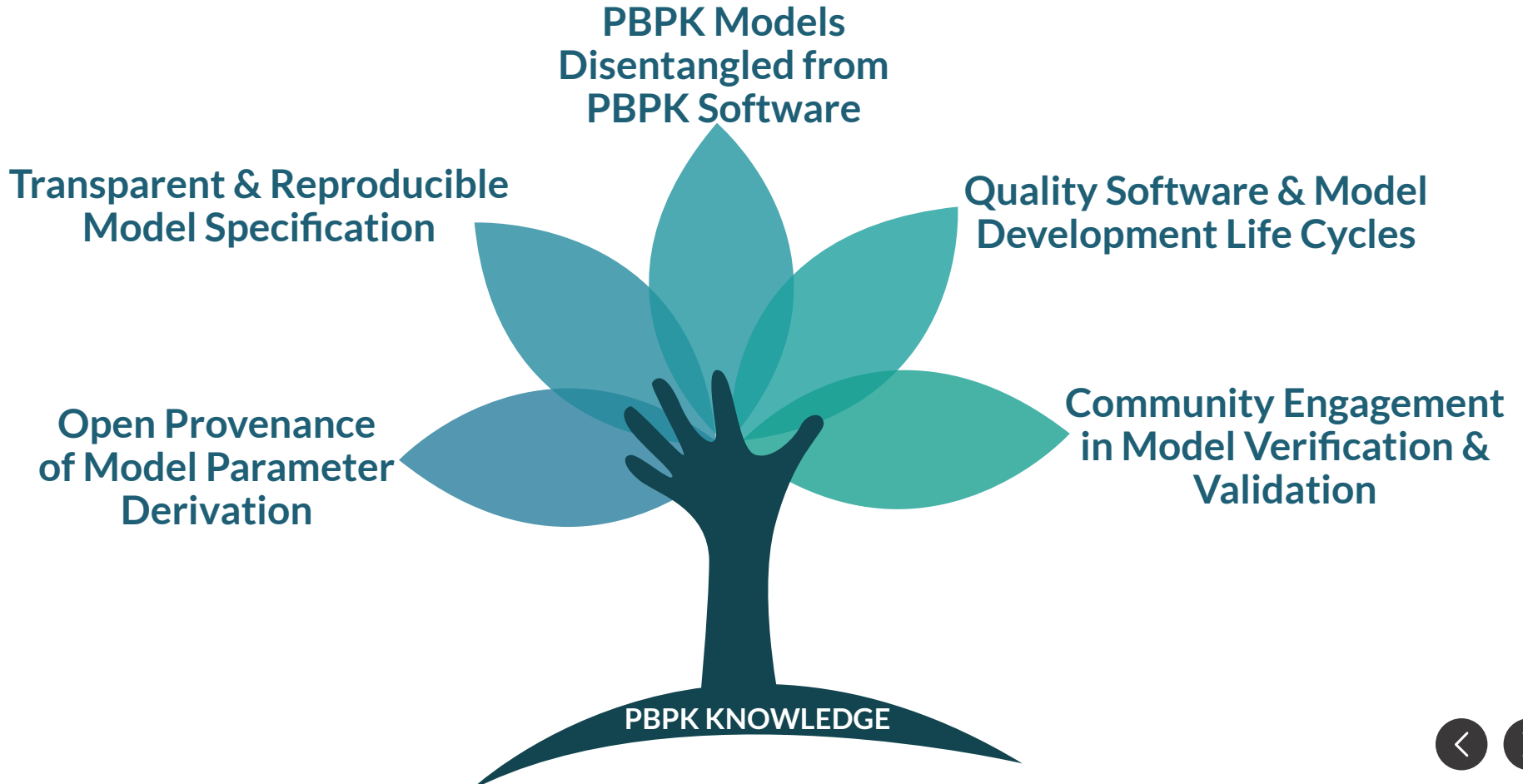
PBPK Models Disentangled from PBPK Software

Separate Software from Science
- Goals are not always aligned

Evaluate Models Independent of Software
- Performance of each is important but should be independently verified and validated

Let Physiology be Free and Open
- Allows for interoperability, accessibility, shared learning

PBPK KNOWLEDGE

Transparent and Reproducible Model Specification

Structural Model Transparency

- Provide complete mathematical specification for the model structure

Statistical Model Transparency

- Provide complete specification of parameters, distributions, and related hierarchical structure

Specific Software Implementation

- Provide complete model specification code set and code for generation of derived tables and figures for the tool or tools used to conduct the work.

PBPK KNOWLEDGE

Open Provenance of Model Parameter Derivation

Define for Each Parameter

- Source, species, units, sample size, precision, disease state, functional relationships, optimized or experimentally derived

Explore Alternative Parameters/Sources

- If available, other cited values or the plausible range of values used in global and local sensitivity analyses

Interoperability Standards

- Develop parameter specification standards for content and format (e.g. XML)
- Allows for automated connectivity with various software tools.

PBPK KNOWLEDGE

Quality Software & Model Development Life Cycle Management

Software Development Life Cycle

- Professional software development standards and best practices
- Peer reviewed
- Iterative or pre-specified requirements, implementation, tests, acceptance, and documentation
- Commercial or open-source

Model Development Life Cycle

- Similar principles and processes applied to model development

PBPK KNOWLEDGE

PBPK Knowledge Growth with Open Science

Community Engagement in Model Verification & Validation

Quality

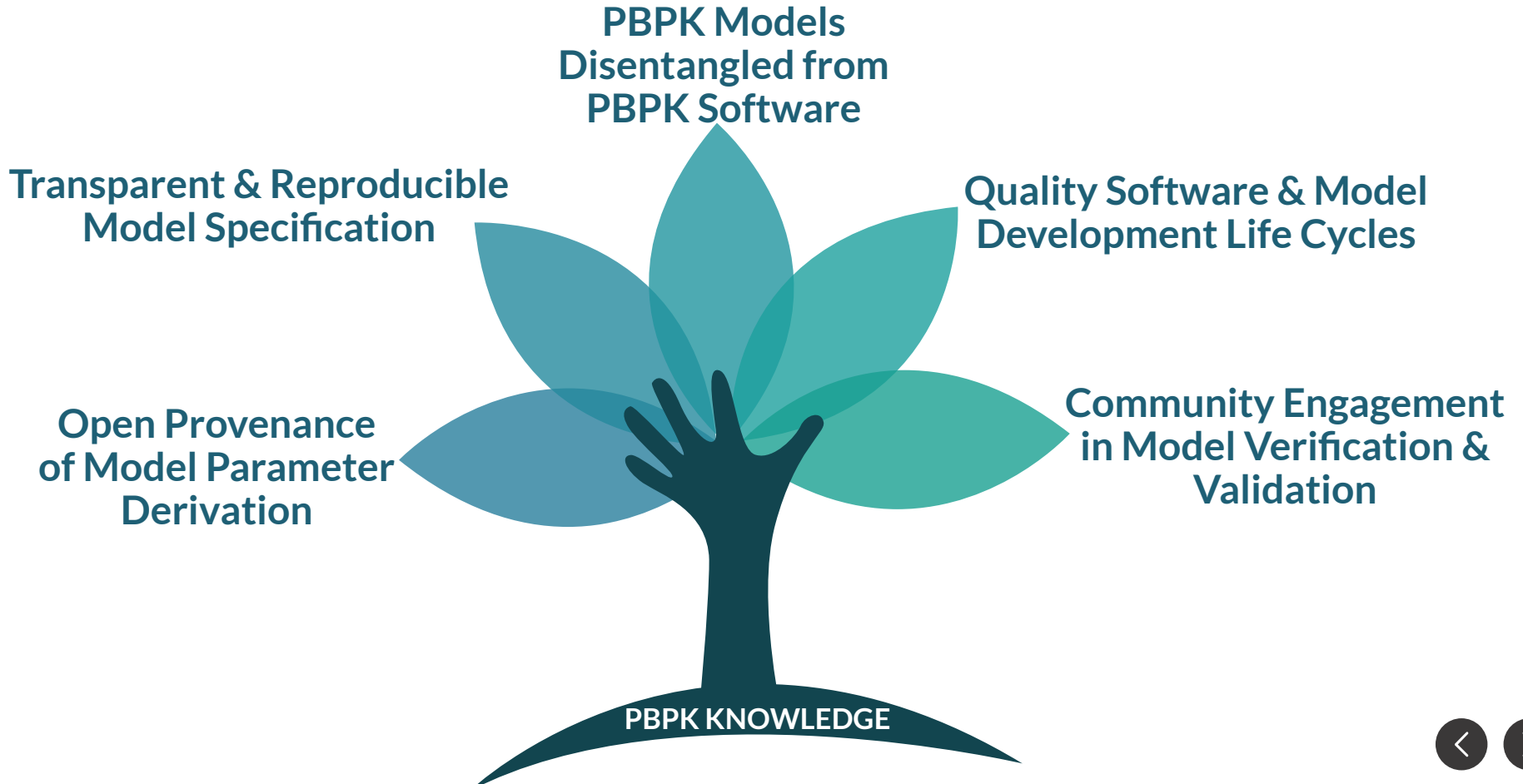- "Given enough eyeballs, all bugs are shallow." -E.S. Raymond

Scientific Relevance

- Allows varied scientific expertise to impact the model

Credibility

- Widespread, documented, qualified testing and use leads to credibility = understanding and documentation of how (and where) the models work (or don't).

PBPK KNOWLEDGE

PBPK Knowledge Growth with Open Science

PBPK Models Disentangled from PBPK Software

Transparent & Reproducible Model Specification

Quality Software & Model Development Life Cycles

Open Provenance of Model Parameter Derivation

Community Engagement in Model Verification & Validation

PBPK KNOWLEDGE

Thank You

Presentation available: https://metrumrg.com/publications/