From cold to hot:
Perception of the use and impact of QSP in immuno-oncology
– A survey of the community and stakeholders –

Vincent Lemaire and Fei Hua
(on behalf of the ISoP QSP I-O Working Group)

Rosa webinar, Jan 18th, 2023

Clinical Pharmacology & Therapeutics

White Paper | Open Access

From Cold to Hot: Changing Perceptions and Future Opportunities for Quantitative Systems Pharmacology Modeling in Cancer Immunotherapy

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The ISoP QSP I-O Special Interest Working Group

Members (at the time of the survey):

- **Fei Hua (Applied Biomath) -- past chair**
- **Dean Bottino (Takeda) – past chair**
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- Vincent Lemaire (Genentech)
- David Bassen (Applied Biomath)
- Mike Reed (Rosa)
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- Andrzej Kiersek (Certara)
- Lei Sun (Alkermes)
- Paolo Vicini (Kymab)

Mission:

- Focus on maximizing impact of QSP in I-O Drug discovery, development, and use in patients.
- Exchange of ideas and pre-competitive knowledges among different companies, academia and clinicians to improve I-O QSP model development.
- Promote mechanistic modeling in I-O and dissemination of modeling in cross-disciplinary forums (in particular for non-modeling scientists and decision makers in immuno-oncology).
- Provide expert feedback and guidance for the modeling community in I-O.

Immune system and cancer

New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

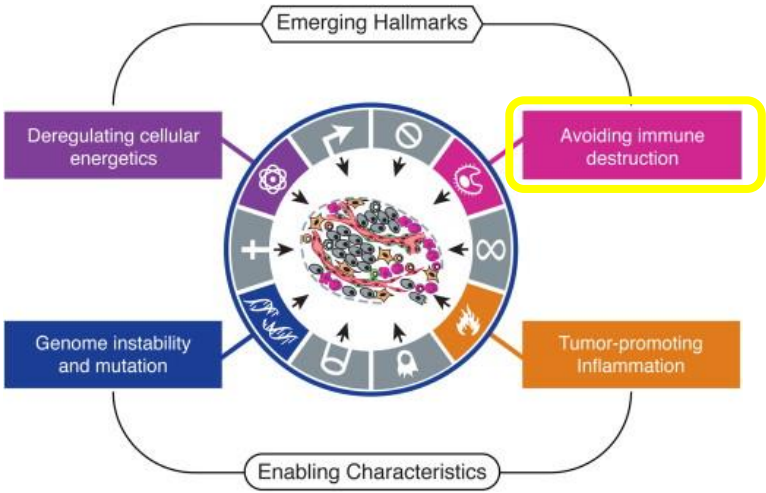
Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York, it came out yesterday that nearly 100 cases of that supposely incurable disease have been cured in this city during the last few years, all through the use of the fluid discovered by Dr. Coley.

Image from following paper: Oiseth SJ, Aziz MS. Cancer immunotherapy: a brief review of the history, possibilities, and challenges ahead. *J Cancer Metastasis Treat* 2017;3:250-61. http://dx.doi.org/10.20517/2394-4722.2017.41

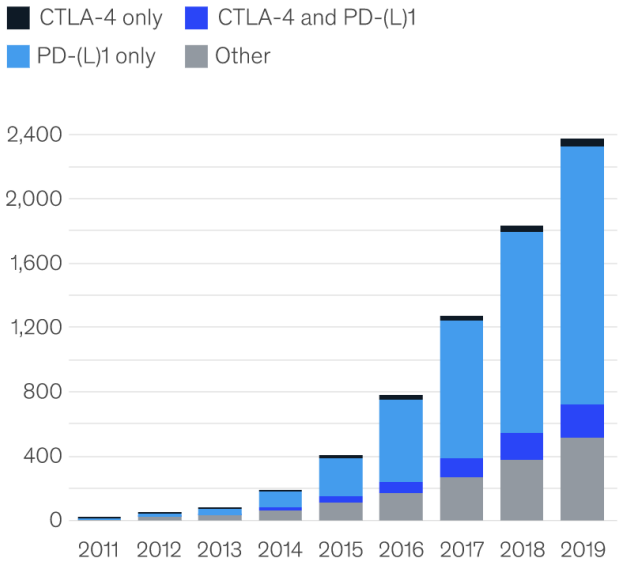
Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]
[1]The Swiss Institute for Experimental Cancer Research (ISREC), School of Life Sciences, EPFL, Lausanne CH-1015, Switzerland
[2]The Department of Biochemistry & Biophysics, UCSF, San Francisco, CA 94158, USA
[3]Whitehead Institute for Biomedical Research, Ludwig/MIT Center for Molecular Oncology, and MIT Department of Biology, Cambridge, MA 02142, USA
*Correspondence: dh@epfl.ch (D.H.), weinberg@wi.mit.edu (R.A.W.)
DOI 10.1016/j.cell.2011.02.013



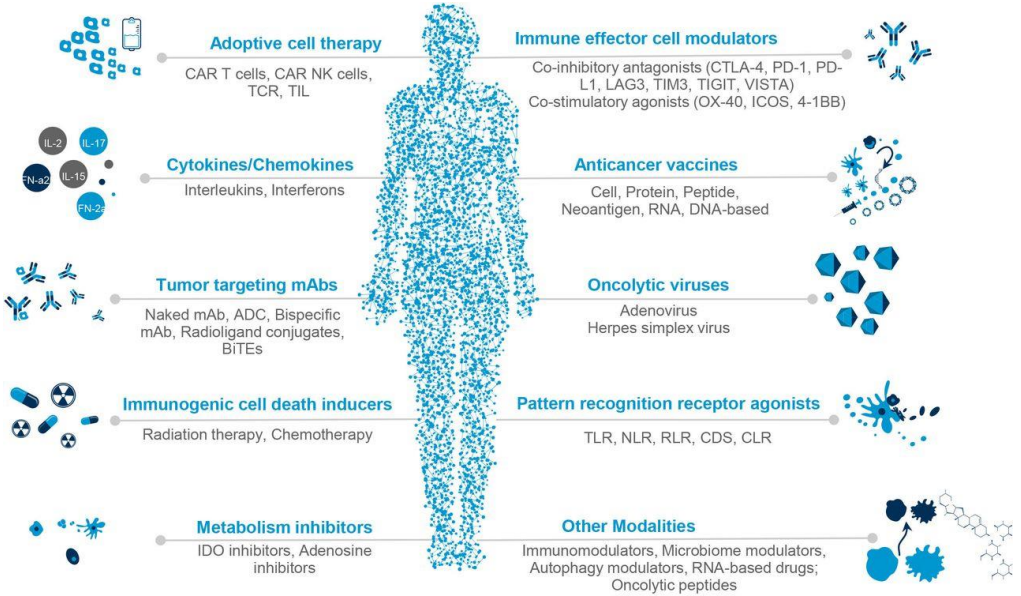
Immuno-oncology has experienced unprecedent diversity, scale, and complexity

PD-(L)1 and CTLA-4 clinical activity



https://www.mckinsey.com/industries/life-sciences/our-insights/delivering-innovation-2020-oncology-market-outlook

Classification of immuno-oncology agents



Franklin MR, Platero S, Saini KS, *et al* Immuno-oncology trends: preclinical models, biomarkers, and clinical development. *Journal for ImmunoTherapy of Cancer* 2022;**10:**e003231. doi: 10.1136/jitc-2021-003231

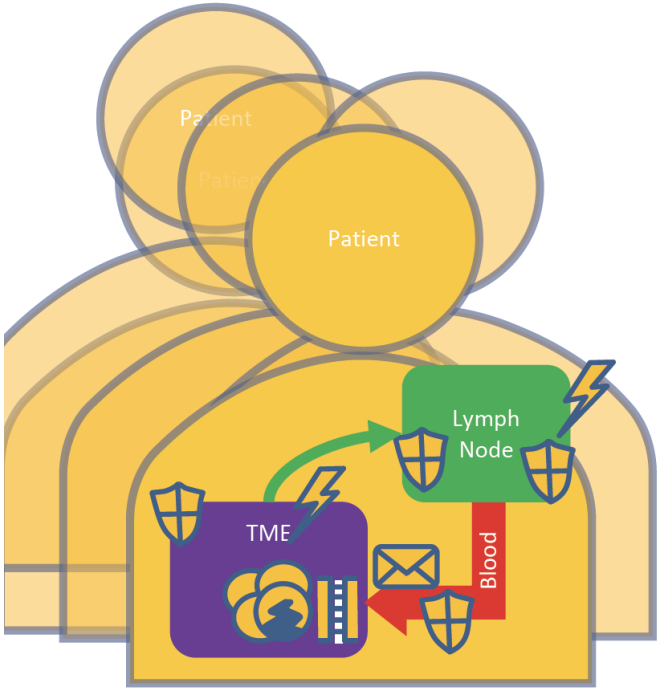
Range of ODE models in drug R & D

Empirical PK/PD
- Try to find a minimal model to describe the observed data

Mechanistic PK/PD
- Integrate the pharmacology of the drug, e.g. binding to targets

Quantitative Systems Pharmacology (QSP)
- Describe disease biology
- Describe downstream effects after drug engagement

Anatomy of IO QSP Model



Population Variability

Patient

Systemic Cytokines

Tumor

Immune synapse

Immune cells

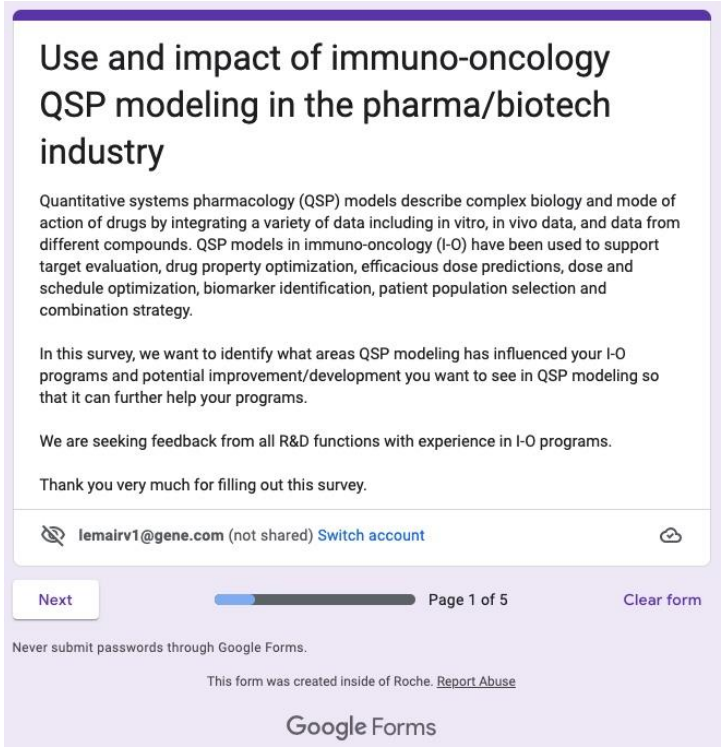
Intracellular pathway

Treatment MoA

Scale

The survey

The survey form was live for 4 months in Feb-June 2021



The goal of the survey was to

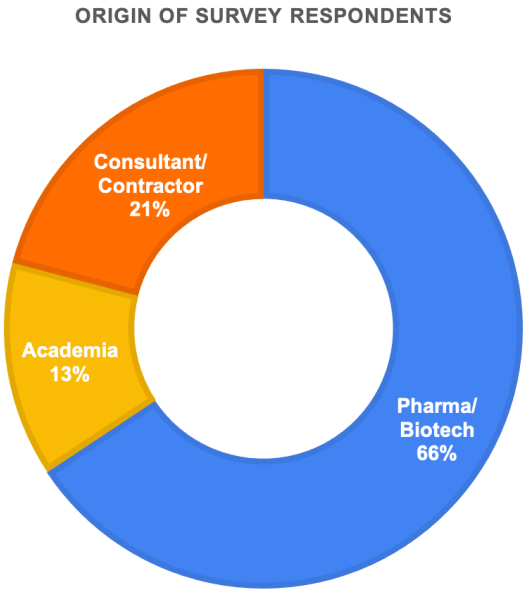
- Evaluate the current impact of QSP in immuno-oncology
- Identify areas of strength and areas that would need improvement
- Get a sense for where the field may be going in the future.

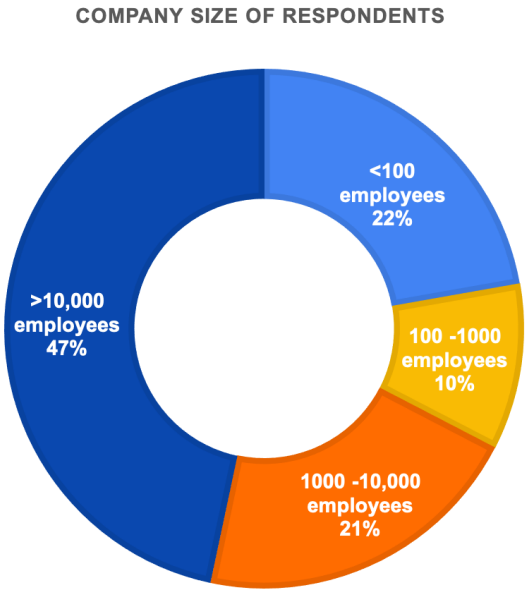
16 questions in 5 categories:

1. Background
2. Current use and impact of QSP in I-O
3. Current challenges of QSP in I-O
4. Future directions of QSP in I-O
5. Additional thoughts

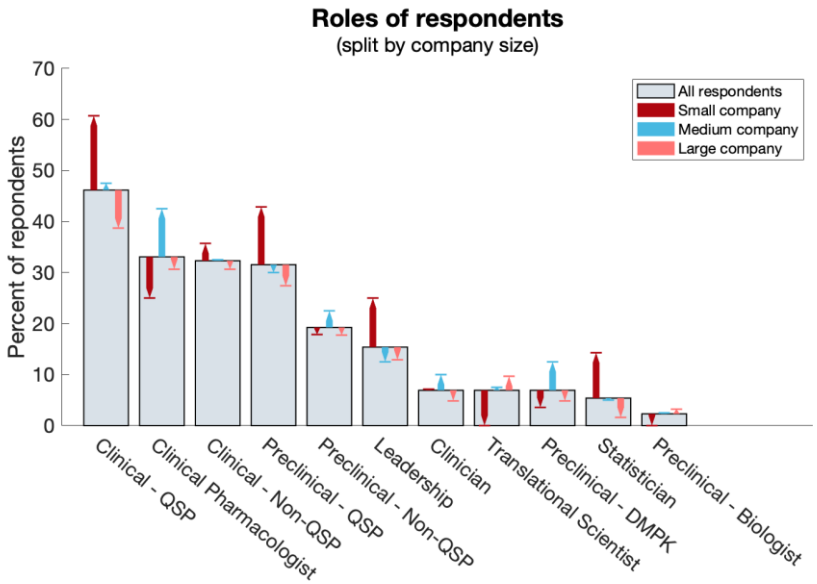
Survey respondents demographics

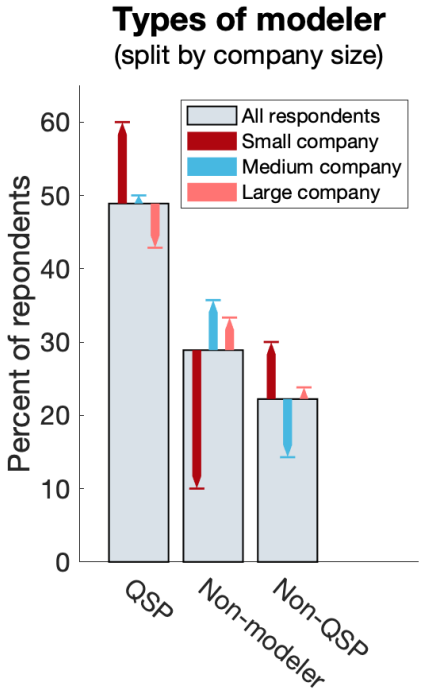
134 respondents from industry and academia





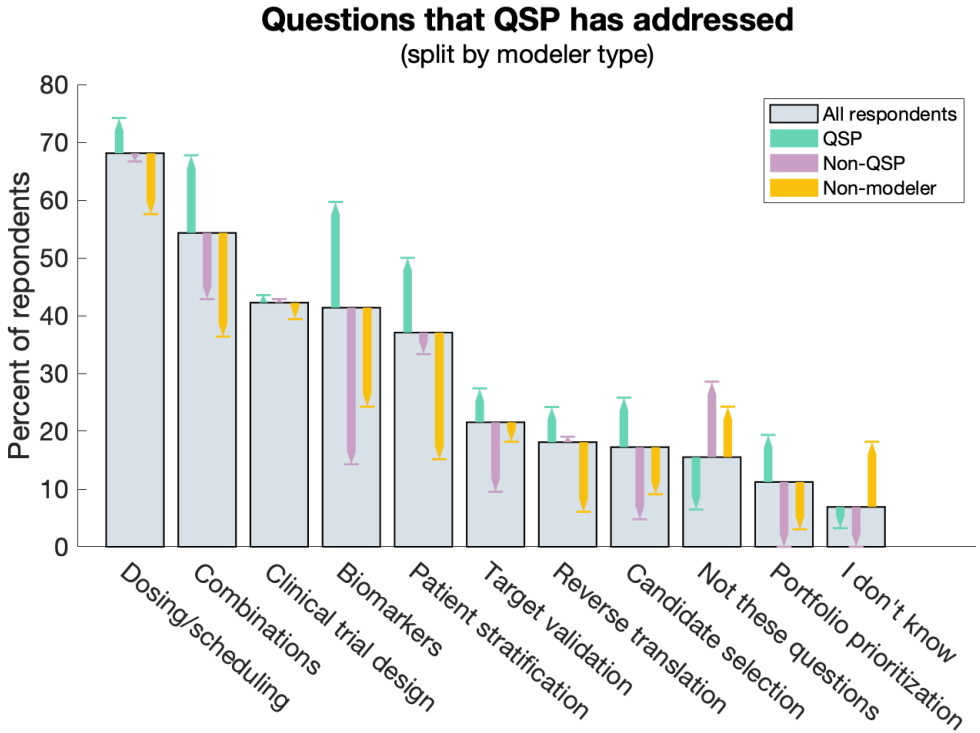
Survey respondents roles





Applications of QSP in I-O

What are the key I-O questions that QSP has already facilitated in your programs?



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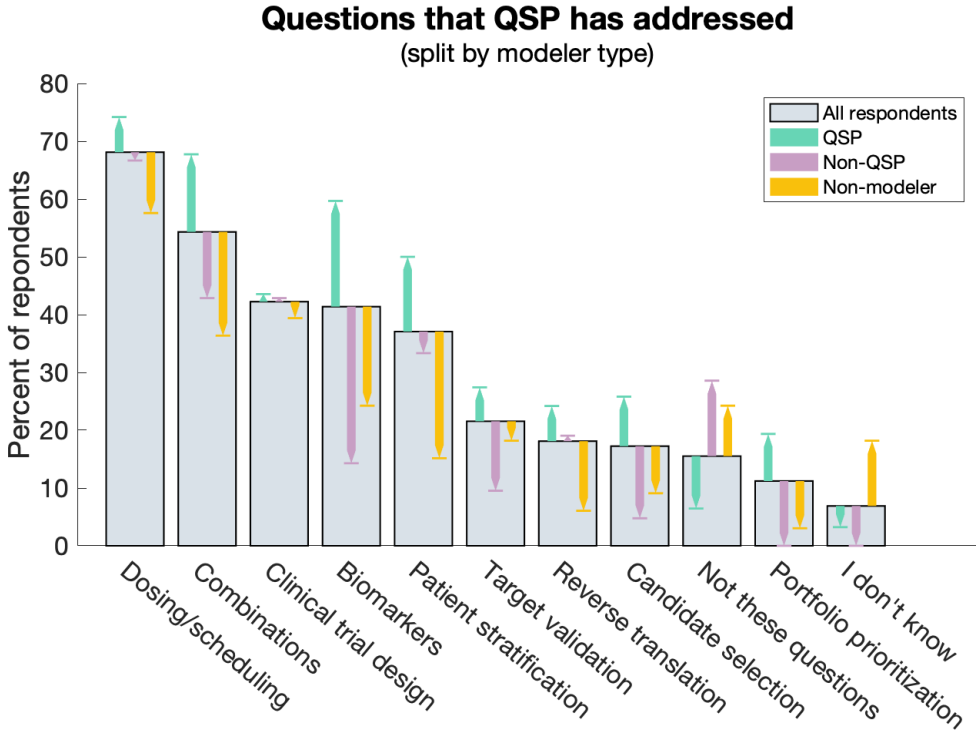

Top areas:

1. Dosing/scheduling
2. Combinations

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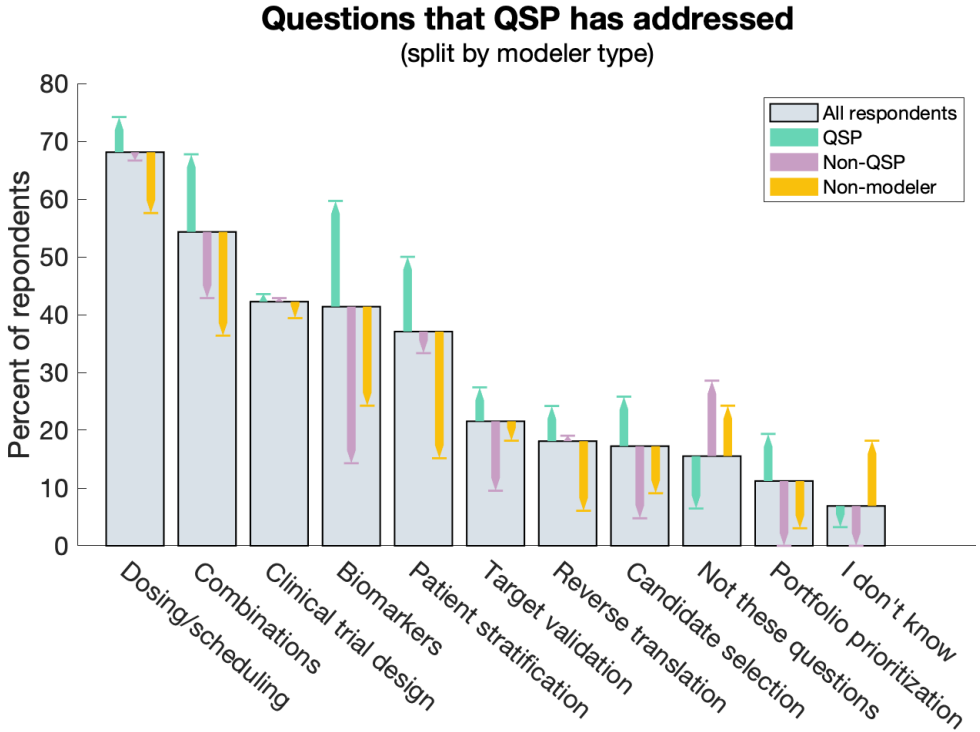

Top areas:

1. Dosing/scheduling[1]
2. Combinations[2]

Top perceived applications correlate well with the frequency of publications in these domains

[1] Hosseini I., at al., 2020., NPJ Syst Biol Appl 6, 28.
[2] Kosinsky Y., et al., 2018. J Immunother Cancer 6, 17

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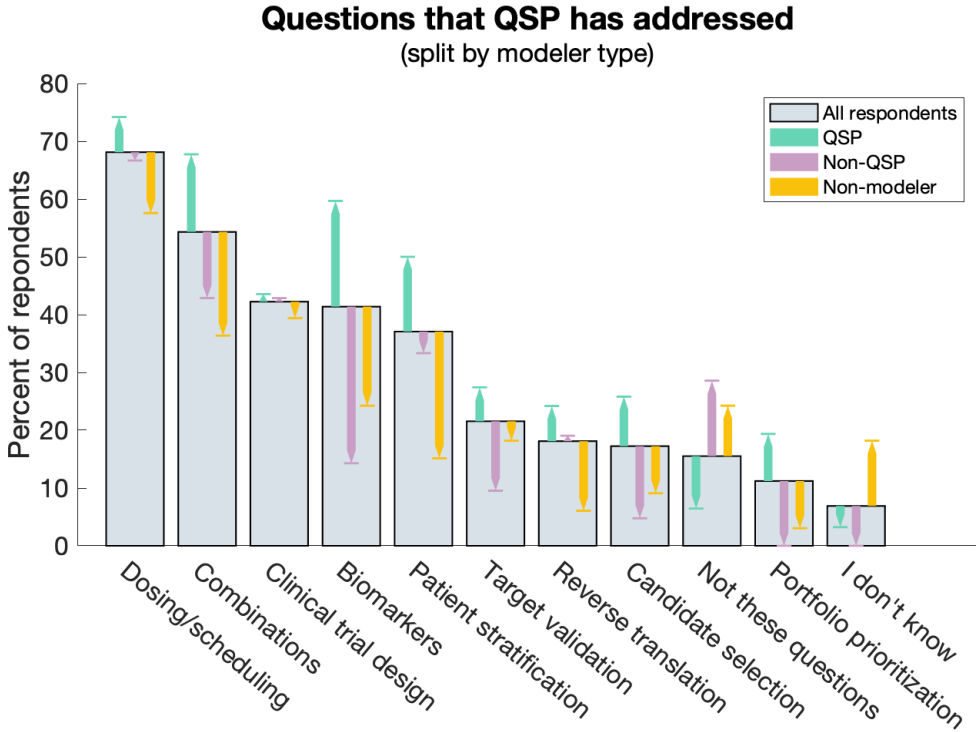

bottom areas:

1. Portfolio prioritization
2. Not these questions
3. Candidate selection
4. Reverse translation
5. Target validation

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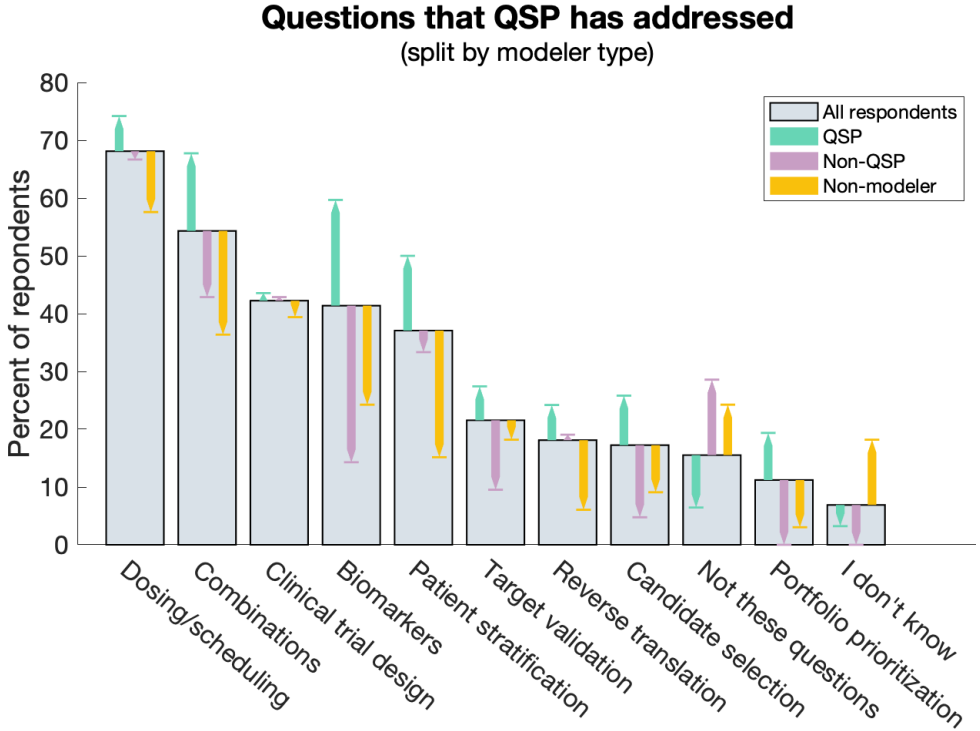

bottom areas:

1. Portfolio prioritization
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Candidate selection & Target validation: Early development

Reverse translation: New area

Portfolio prioritization: Strategic decision based on multiple inputs

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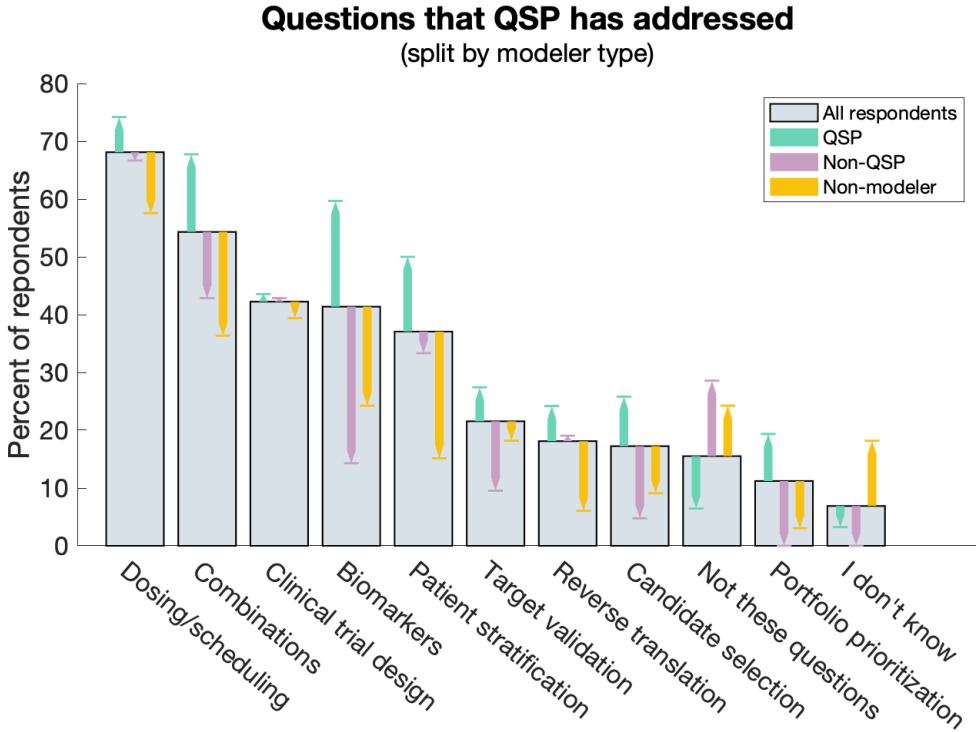
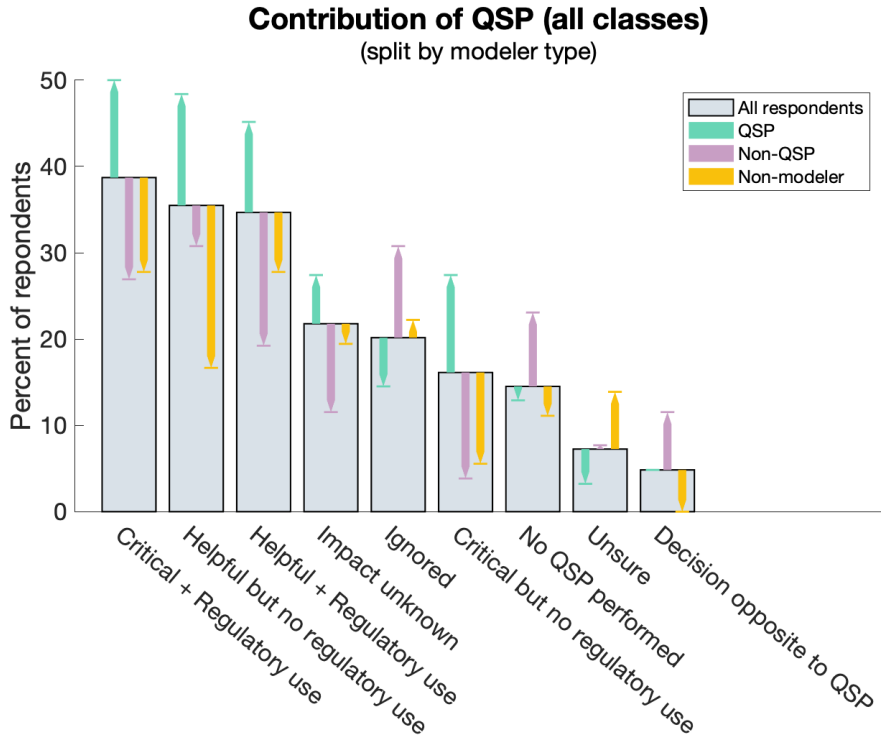


Most conflicting areas:

1. Biomarkers

Perceived impacts of QSP in I-O

What have been the contributions of QSP in your I-O projects?



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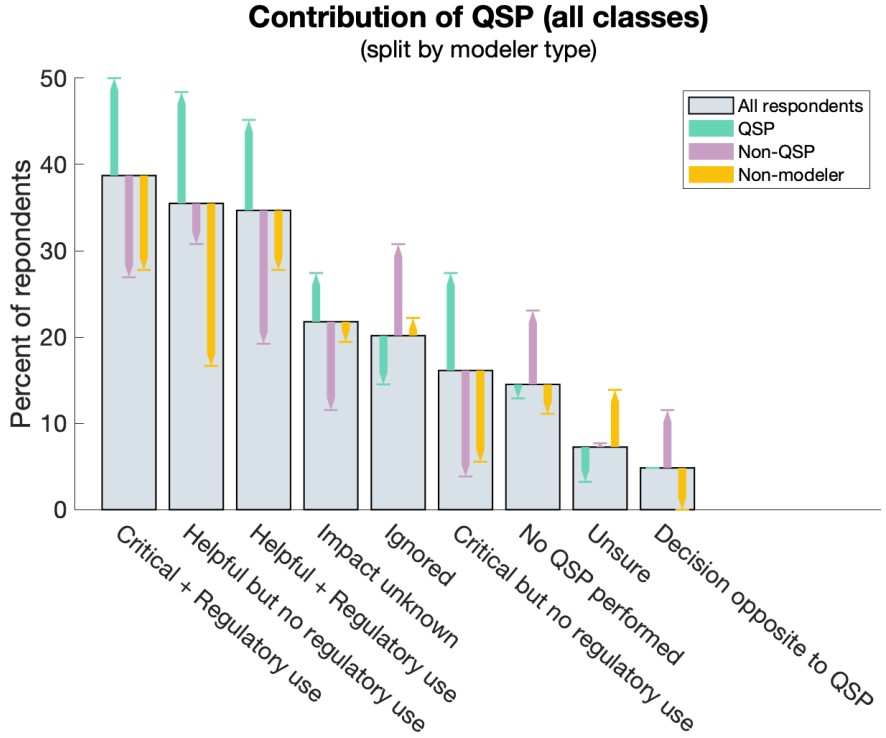

Top impacts:

1. Critical + Regulatory use
2. Helpful but no regulatory use
3. Helpful + regulatory use

The survey respondents perceive the contribution of QSP positively, with most of the responses ranging from QSP leading to critical impact on projects to being useful to projects

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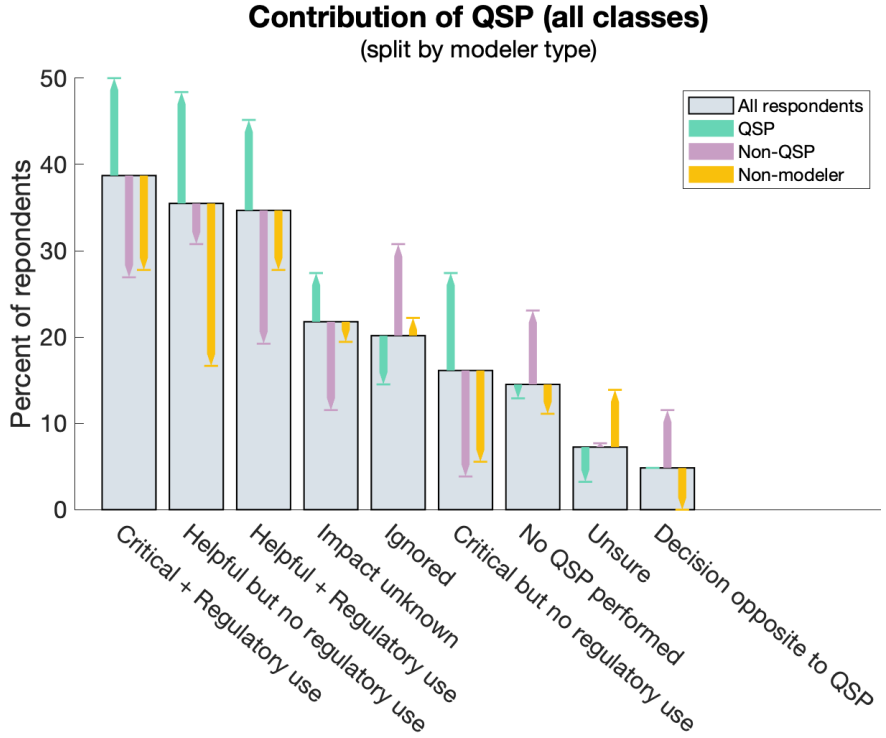

Bottom impacts:

1. Decision opposite to QSP
2. Unsure
3. No QSP performed

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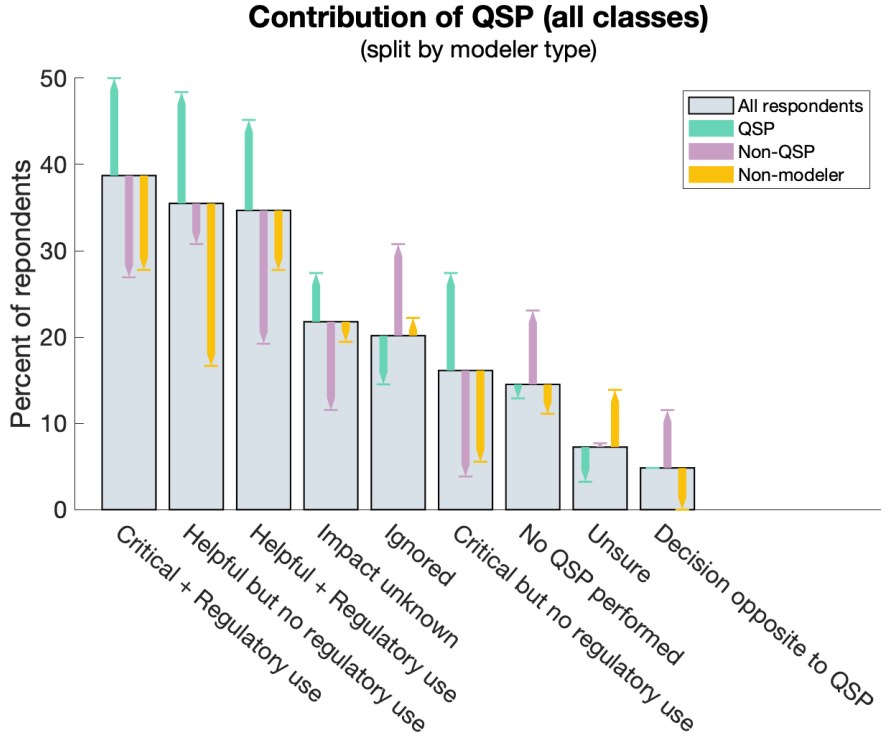

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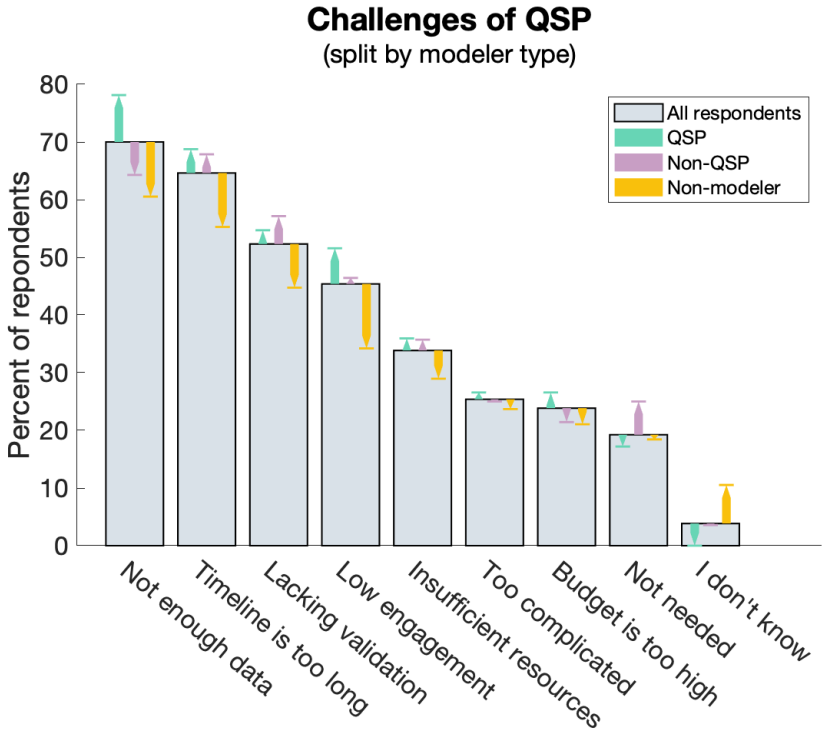
Challenges of applying QSP in I-O

What are the challenges in applying QSP modeling to support I-O projects?



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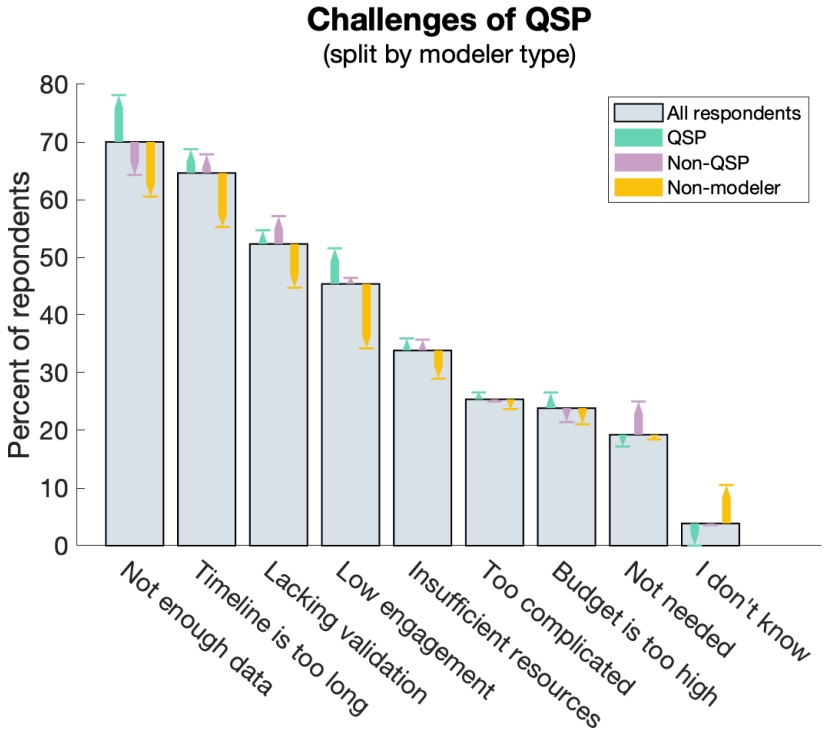

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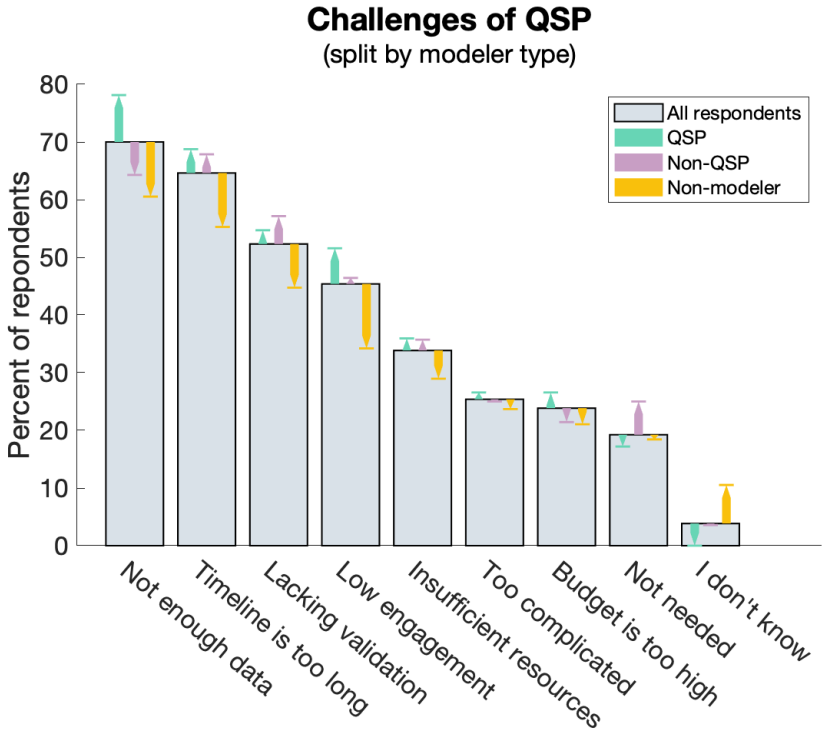

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Not enough data: Widespread difficulty for all modeling approaches

Timeline is too long: Complexity

Lacking validation: No generally accepted validation process

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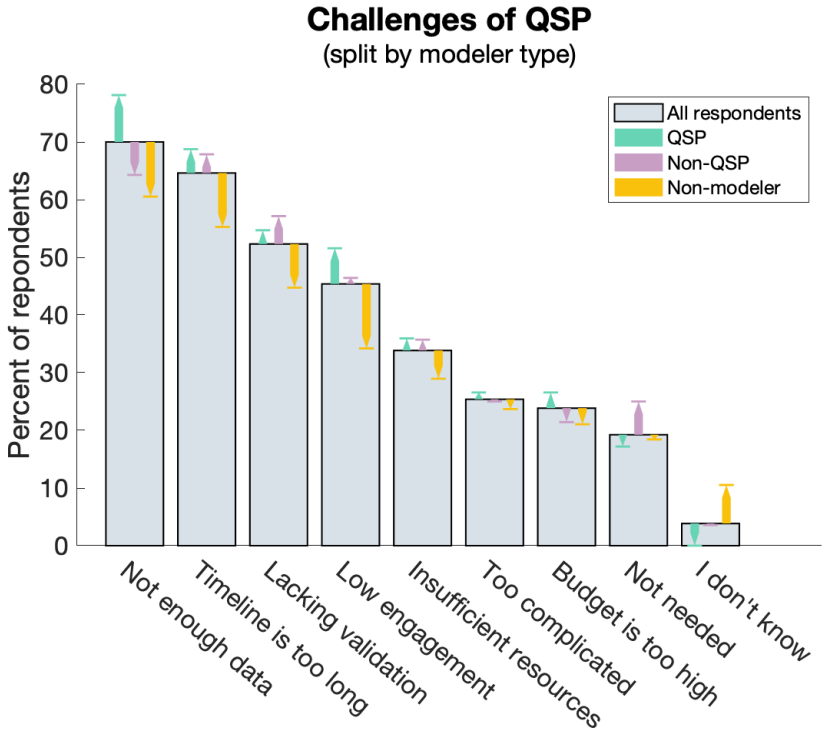

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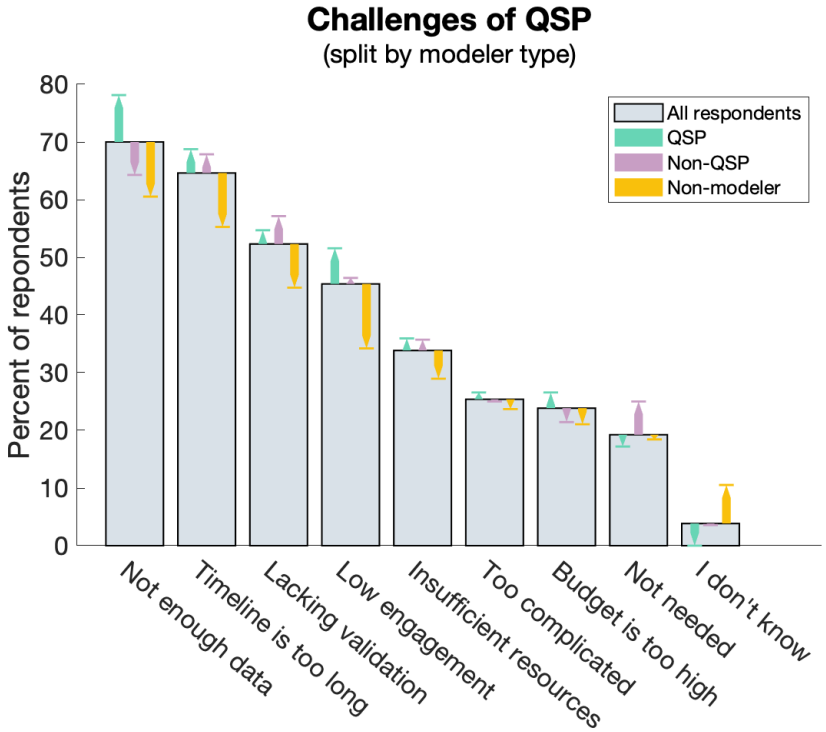

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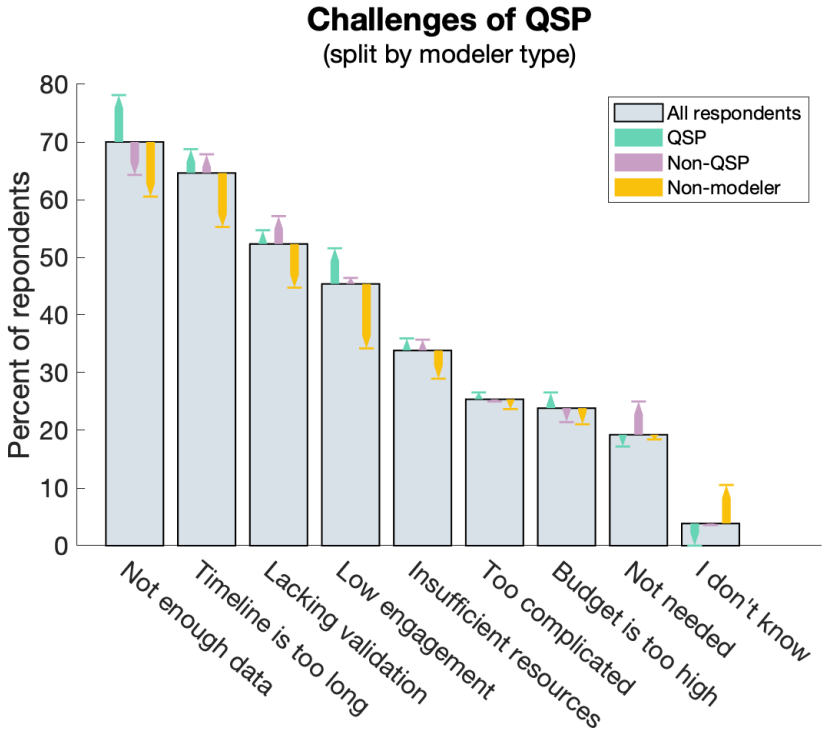
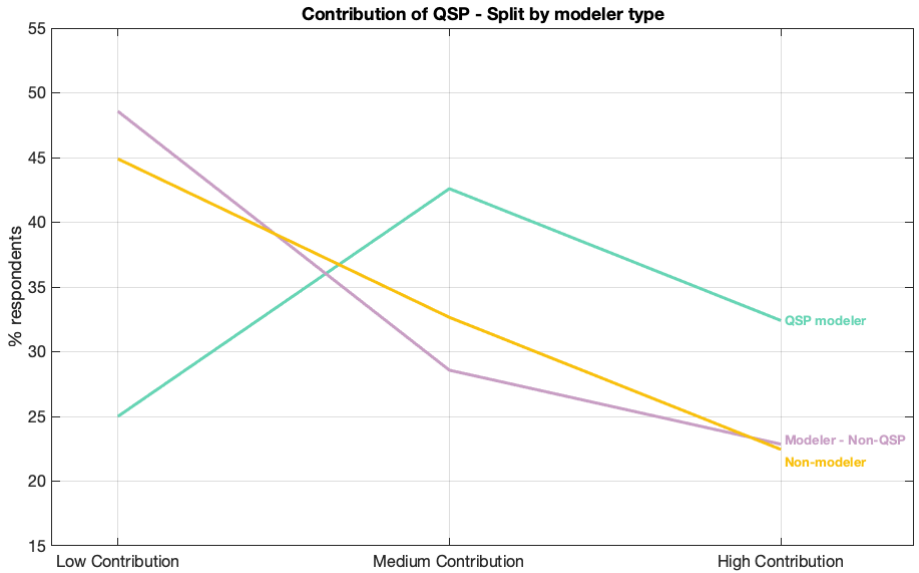
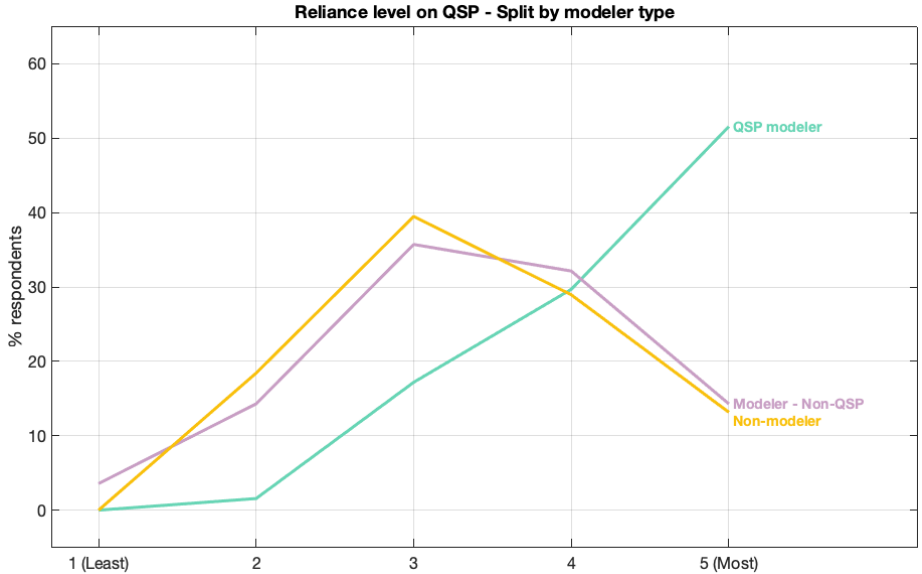


Bottom Challenges:

1. Not needed
2. Budget is too high
3. Too complicated

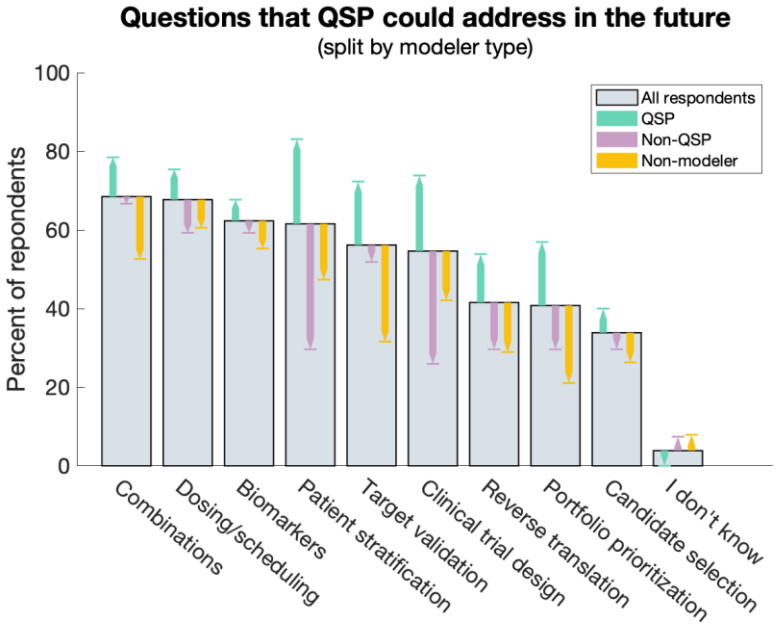
Difference in perception between QSP modelers and non-QSP people

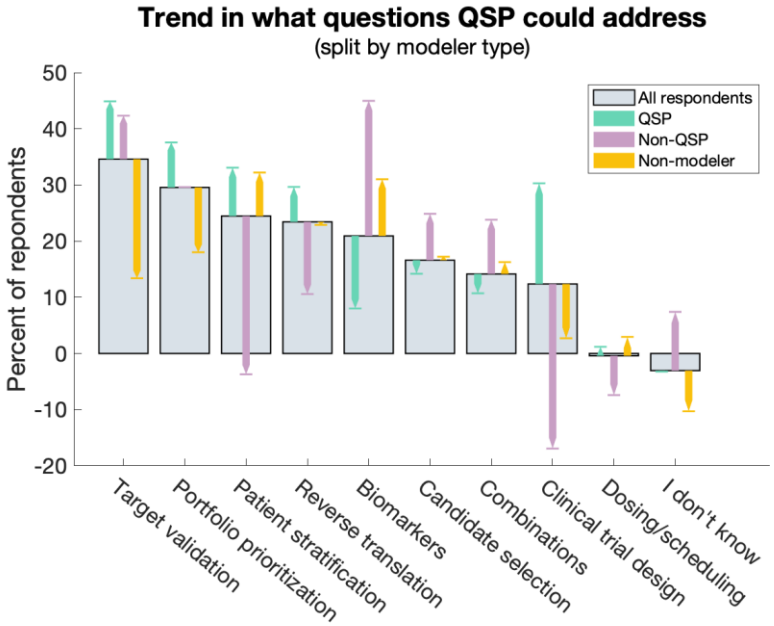




Future directions of QSP in I-O

What are the key I-O questions that QSP could address in your programs in the future?





Unique aspects of applying QSP in I-O vs. other disease areas

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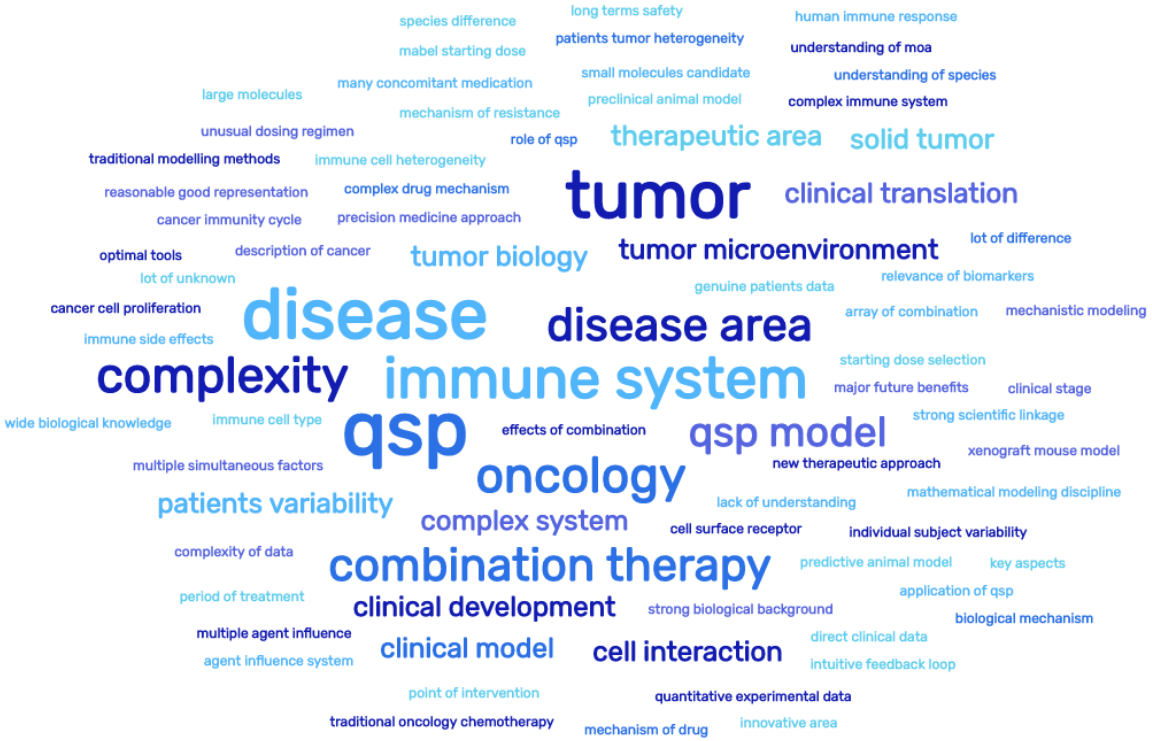

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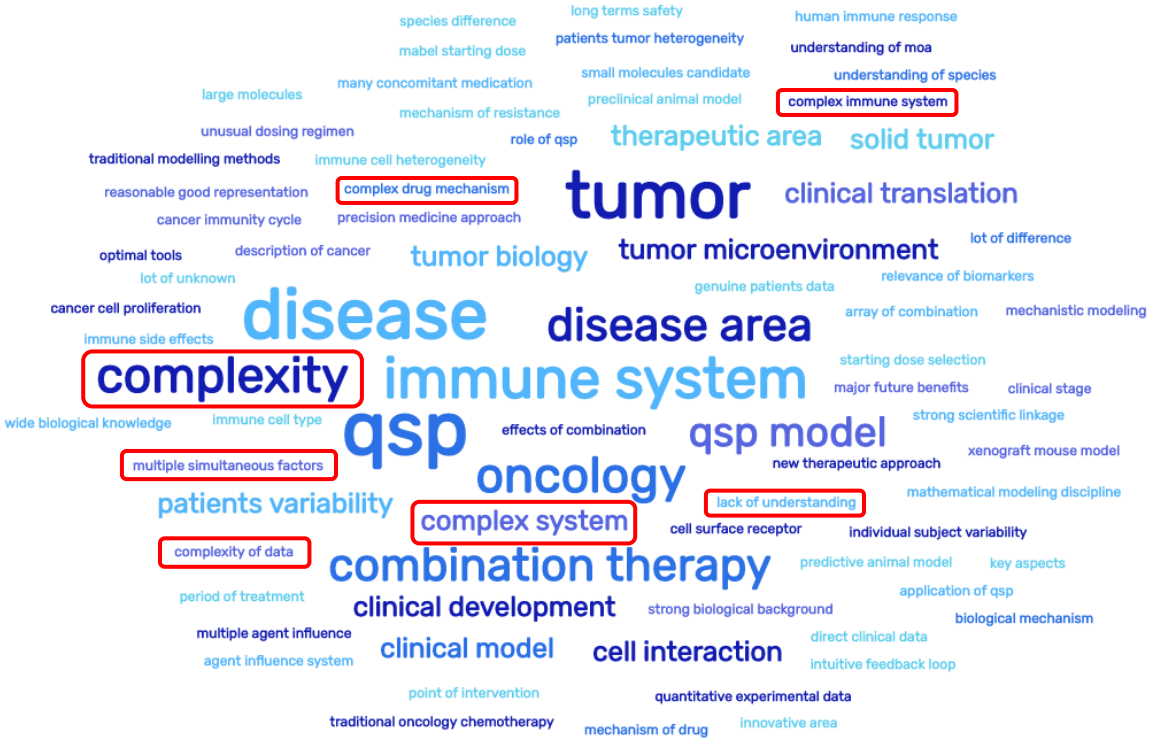
Complexity



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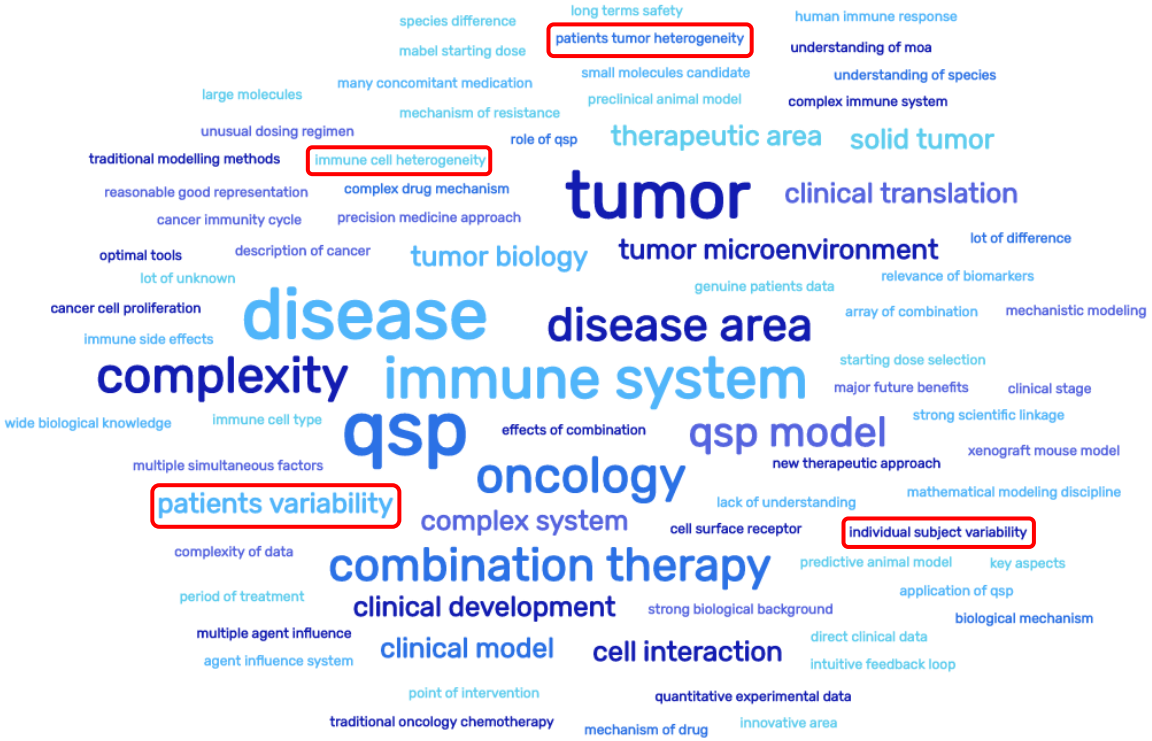
Variability



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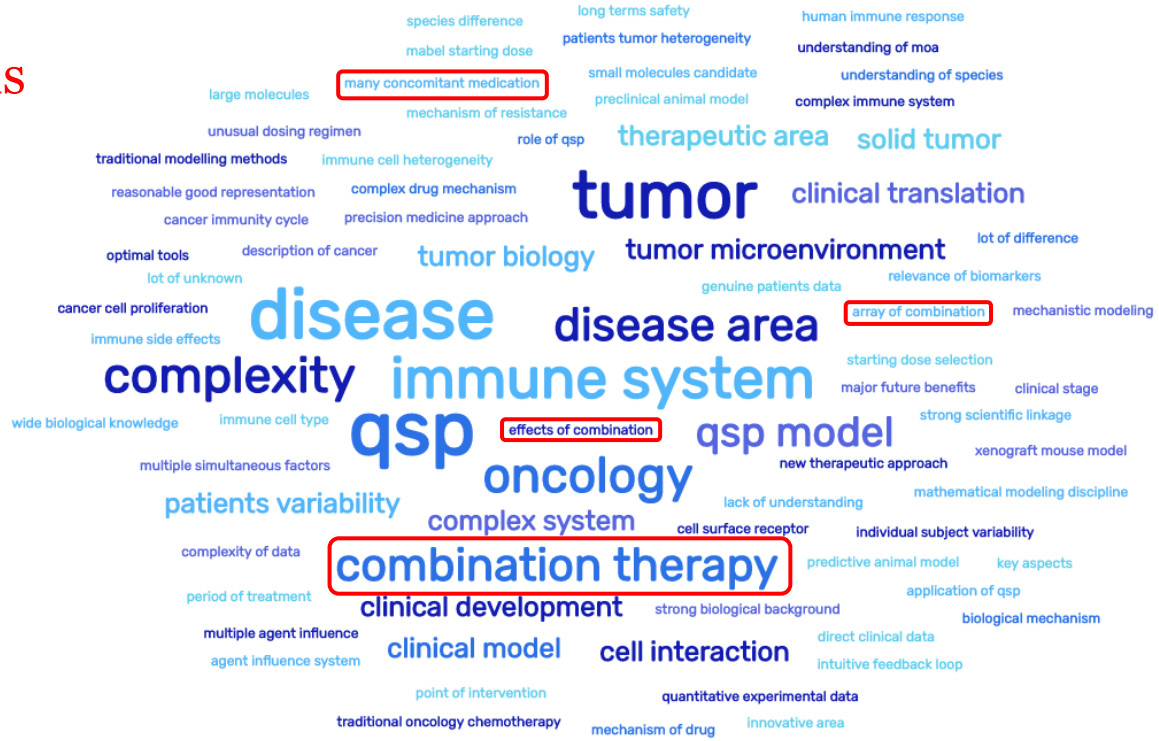
Combinations



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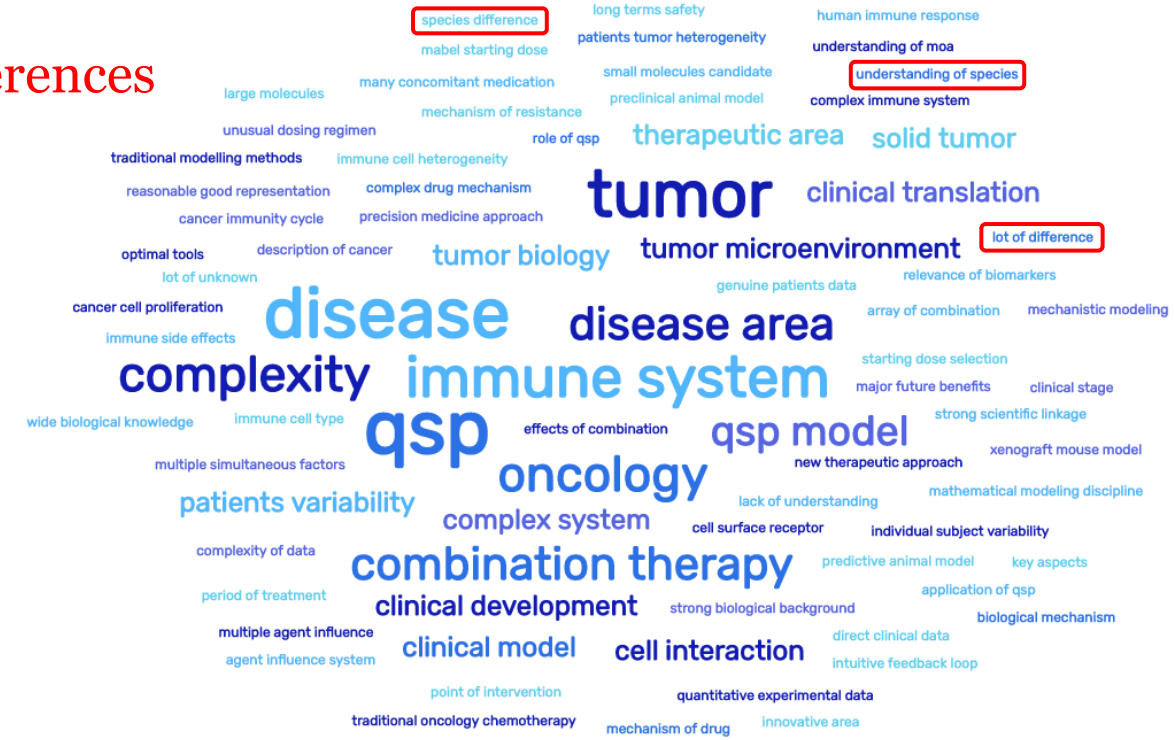
Species differences



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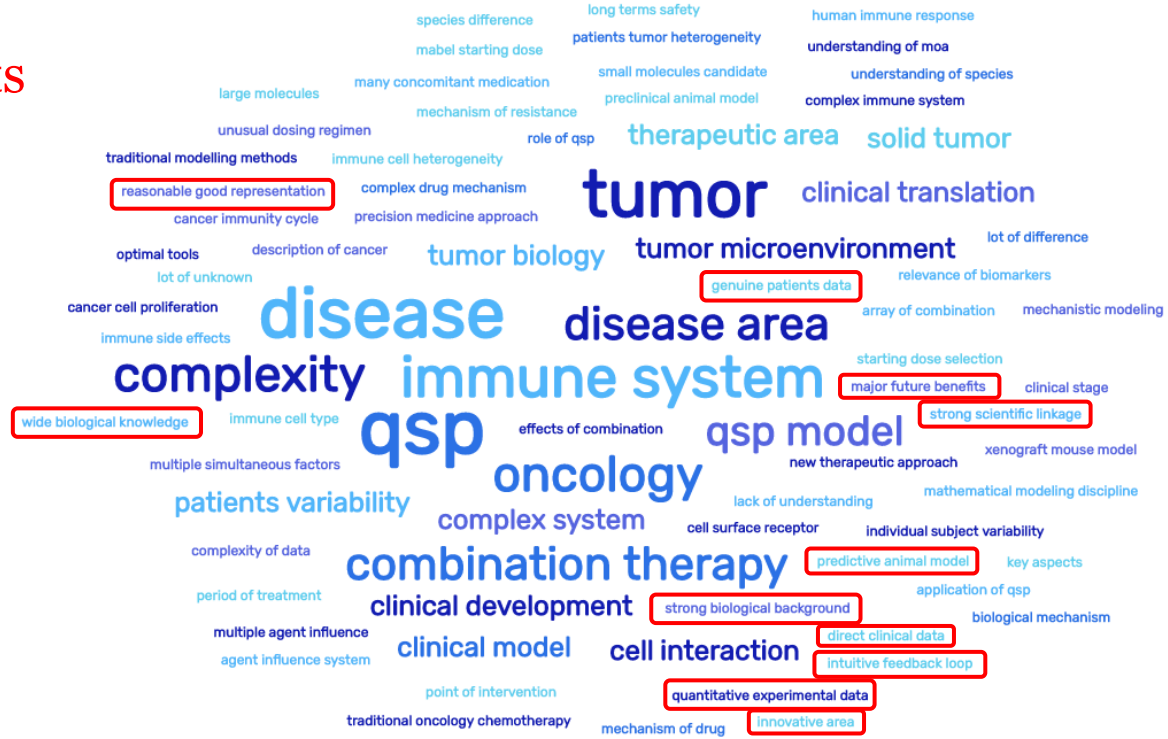
Other aspects



Key takeaway from the survey results

- Overall, the survey respondents perceive the contribution of QSP positively, with most of the responses ranging from QSP leading to critical impact on projects to being useful to projects.
- QSP models seem to be currently most often used to help with dosing/scheduling of clinical studies; while use in early drug discovery such as target validation and candidate selection is lower at the moment but is expected to grow in the future.
- The top 3 challenges for IO QSP model development identified in the survey are limited data, long timeline and insufficient validation of the models.
- The survey revealed differences in perception on the impact of QSP in I-O between QSP modelers and others suggesting QSP modelers need to improve education and communication to their stakeholders.
- For the future, people in general consider that QSP models can further increase their contribution to IO programs in all areas; while helping with combination therapy is being selected by the highest number of respondents.
- A lot of room to grow, either in terms of communication, applying QSP more widely, more transparent validation criteria.

THANK YOU!