Ethical and Welfare Considerations Regarding Precision Animal Modeling

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The Academies’ panels and workshops often explore emerging technologies with an eye to *anticipatory governance*:

Strategic, policy-oriented planning for *risk reduction and management*, using predictive processes to identify key decision points and necessary steps to manage the development, application, and effects of new technologies.
Timing is crucial:

Too early in the technology’s lifecycle, there is not enough known about it to predict its likely future manifestations, potential applications, and possible effects.

But more mature technologies may be too widely diffused to manage effectively through professional norms and standards, formal policy and regulation, and public opinion.

Where we are in terms of anticipatory governance of animal modeling for precision medicine is not clear. This workshop will contribute significantly to answering that question as well as to defining possible frameworks and elements for such future governance.
Consideration of ethics and values is essential for anticipatory governance.

Professional ethical standards of practice shape how new scientific developments unfold and inform how they are applied.

The public’s diverse values support – or oppose – scientific developments and new technologies, often from distinctly different perspectives than those of the scientific community.

Public engagement is a key theme of the Precision Medicine Initiative, but not necessarily regarding the supporting role of animal-based research.
Ethicists, like most other participants in anticipatory governance, are challenged by the need to predict how a technology will develop and be applied.

Typically, clear ethical standards in science have been articulated *retrospectively*, after a crisis or scandal or dramatically new capability challenges the status quo.

Ethicists must rely on others’ reports about new scientific developments to identify their potential ethical impact and make recommendations about their ethical use.

Discussion of animal models in precision medicine is still too new to have generated a related ethical discourse.
The first outline of where precision medicine will need research with model organisms was published only last year:

- Interpretation of gene variants
- Incorporation of “-omic” data
- Evaluation of effects of environmental exposures
- Development of integrative in vivo modeling

Lloyd KCK, Robinson PN, McRae CA. Animal-based studies will be essential for precision medicine. *Science Translational Medicine*, 2016, 8 (352)
Returning to basics: Defining precision medicine

Precision medicine is “data driven treatment and prevention” that “takes into account individual variability in genes, environment, and lifestyle for each person.”

https://ghr.nlm.nih.gov/primer/precisionmedicine/definition
Returning to basics: defining Precision Medicine and how animal models may be used

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Consideration of ethics and welfare in animal research to support precision medicine will need to include:

- The reliability, sharing, and use of animal data
- Modeling genetic effects
- Modeling environmental effects
- Modeling lifestyle, social, and behavioral effects
Returning to Basics: The 3 Rs

Researchers should use animals of the lowest level of evolutionary complexity and consciousness possible to answer the question and *replace* animal models with alternatives whenever possible.

Protocols should be based on thorough knowledge of past work and designed to *reduce* the number of animals and experiments to the fewest necessary to answer the research question in a statistically significant way.

Researchers should continuously *refine* their procedures to eliminate or at least minimize animal pain and distress.
Precision medicine’s *data-driven* work will depend on large databases for human AND animal research.

Collaborative databases support reduction and replacement:
- WormBase
- FlyBase; Mt. Sinai’s Center for Personalized Cancer Therapeutics’ database of fruit fly tumor avatars and effective chemotherapy
- Zebrafish International Resource Center (ZFIN)
- The Knockout Mouse Project; International Mouse Phenotyping Consortium; International Mouse Strain Resource
- Immuno Polymorphism Database/Non-Human Primates Database

Ethical norms and best practices in data sharing generally are still being defined and adopted. Funding is needed to establish databases, and for them to coordinate systems, standardize formats, validate information, and support communication between animal and human research.
Studies on environment-gene interaction will challenge housing standards, especially for animal models of illness linked to complex environmental exposures: e.g., multiple pollutants, “sick buildings”, noise.

Some animal studies on environment-gene interactions may appear to seek clinical or physiologic information on problems for which public health solutions already exist, running counter to the goal of reduction.

Even refined, such animal studies risk injustice to humans: How much industrial pollution does it take to trigger genetic determinants? Can a drug be developed to counter a pollutant’s effects on heart health?
Studying the effects of gene-lifestyle interactions will need to distinguish carefully between behavior – which in humans is typically considered volitional and subject to change – and environment, which is presumed not to be.

How might a model for volitional cigarette smoking differ from one for chronic exposure to wood smoke?

Interactions between genes and volitional behaviors may require the use and development of more sentient animal models than would be needed to study environmental effects, conflicting with the goals of replacement.
The goal for refined, early endpoints in animal studies creates tension with the need for longitudinal data for humans with prolonged, chronic, and terminal illness.

Studies on diseases linked to poverty will need to expose animal models long term to harmful environmental factors and stressful social settings that conflict with animal housing and enrichment standards.

Similarly, many of today’s successes in precision medicine, e.g., in treatment of advanced cancer, come at the end of life, past the point where research animals would be humanely euthanized.
Researchers, research institutions, and funders need to look for and recognize old, new, and potentially unexpected ethical issues in the innovative use of animal models in precision medicine research.

- Front line researchers
- IACUCs and IRBs
- Journal editors and reviewers
- Grant review panels and funding agencies
- Patients and families that participate in human trials

Precision medicine’s ethical commitment to public engagement will be fully realized only if engagement includes attention to the role of animal research in individualized human care.
Thank you.