POLICY

Translational research and the U.S. federal elections

Translational research is the process of generating new materials and medical evidence for addressing health care needs. Although primarily a scientific activity, governmental policies play an important role in promoting translational research and aligning this effort with health priorities. Policies relating to translational research are often discussed by leaders of executive and legislative bodies, usually in the context of broad statements regarding certain initiatives (for example, the Cancer Moonshot), research funding, and the selection of science advisers. Candidates for these positions sometimes also give insight into how they would handle biomedical science and innovation policy in their administrations. As the 2016 U.S. presidential and congressional campaigns enter the final stretches, we highlight several priority areas along the trajectory of clinical translation that candidates in these races should address.

BASIC RESEARCH

All electoral candidates should present their plans for public funding of basic research, which includes the identification of new drug targets, disease processes, and therapeutic platforms. However, basic science is not well supported by the private sector, and public funding continues to constrain the horizon of possibility. In the last year, the U.S. Congress ended 12 years of budgetary stagnation at the U.S. National Institutes of Health by appropriating a 6.6% increase. Yet in real dollars, the increase merely brings funding back to 2003 levels, and uncertainty remains about future appropriations. We encourage candidates to explain what they will do to support basic science funding and how they would ensure sustained expansion of federal support. Those who are unwilling to commit to increased direct government funding should explain how they would otherwise support the sorts of high-risk research activities that open new vistas for clinical application.

A second issue warranting attention from candidates concerns mechanisms for resolving ethical controversies, such as the permissibility of introducing genetic modifications into the human germ line, or the oversight of research involving human cells that can self-organize into embryo-like structures. Whereas elected national government officials might not need to elaborate their personal opinions on such intricate issues, candidates should describe how they would approach policy-making in ethically contentious arenas. Would they cede debates to elected representatives and venues such as the U.S. Congress? Would they draw on advisory bodies, like the U.S. National Academy of Sciences? Or would

they devise structures that involve extensive public consultations before enacting policy, similar to the U.K.'s approach to resolving concerns around mitochondrial replacement techniques (*1*)?

PRECLINICAL RESEARCH

Translational research consumes large quantities of human and material resources, especially in the late phases of testing. These investments are only as sound as the evidence supporting them. Many commentators have cataloged a series of deficiencies in the way preclinical research is conducted and reported.

Although the validity and reliability of preclinical research belongs in the bailiwick of science itself, elected representatives have plenty of opportunities to foster a culture of reproducibility. For example, legislators might push for the creation of prospective preclinical registries that do for animal studies what ClinicalTrials.gov has done for clinical trials. Such preclinical registries would encourage greater prespecification of hypotheses and would promote transparency. Funding bodies could condition transfer of government research funds on the creation of what has been called "good institutional practice" policies at academic medical centers (for example, creating institutional policies that monitor researcher adherence to reporting guidelines or that reward researchers who share data or conduct studies according to rigorous methodological standards) (*2*). Animal care regulations could be amended to articulate an expectation that preclinical studies should be designed with sufficient power to support valid and reproducible claims and that the results of all informative preclinical experiments are published (*3*).

CLINICAL RESEARCH

Problems related to data access and ownership can hinder the conduct of clinical trials. Only a fraction of the evidence generated in clinical trials is accessible to the broader research community. For example, 78% of efficacy studies submitted to the U.S. Food and Drug Administration (FDA) for approved new drugs are published, but only 37% of clinical trials for products that never reach licensure are published (*4*, *5*). This uneven and delayed flow of information slows progress and can lead to the persistence of mistaken theories about the therapeutic activity of particular strategies.

Candidates should describe how they plan to influence these trends by articulating policies that would promote data transparency. They should, for example, support enforcement of existing disclosure policies (one study reports that

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only 22% of clinical trials registered on ClinicalTrials.gov have deposited results as intended) (6) or make clinical study reports publicly accessible for all products submitted to the agency in support of a licensing application (the approach taken by the European Medicines Agency).

Candidates might also weigh in on how they view the sharing of individual patient data from clinical trials. Federal funding bodies could withhold funding from institutions that do not make public the results of trials they host. Of course, transparency policies should have limits. Poorly crafted systems for sharing individual patient data, for example, could create opportunities for firms pursuing self-interested and biased secondary analyses; they might present risks to the privacy of patients; and they could diminish professional and economic incentives for pursuing highly innovative research. Candidates who recognize the value of transparency would therefore also need to describe how they would mitigate such liabilities.

Strong human protection policies are key to sustaining the trust and engagement of patients and caregivers in the clinical research enterprise. Whereas the scientific and social environment in which clinical trials are pursued has undergone enormous changes in the past few decades, U.S. human protection policies have stayed relatively static. Developments that strain current human protection policies include a growing volume of research conducted in practice settings, the use of new methods like cluster randomization (which applies randomization to whole medical institutions rather than to individual patients), or the use of clinical trials to promote company products rather than resolve pressing clinical questions (so-called seeding trials). Recently, a U.S. National Academy of Sciences report urged Congress to empanel a body to revisit the seminal document for U.S. research regulations, the *Belmont Report* (www.nap.edu/catalog/21824/optimizing-the-nations-investment-in-academic-research-a-new-regulatory). Candidates should explain where they believe human protections are deficient and how they might modernize oversight policies. Alternatively, candidates who favor the status quo should explain how they intend to alleviate these concerns while preserving current human protection policies.

DRUG LICENSING

Some commentators view drug regulation and innovation as a zero-sum game. Although excessive bureaucratic requirements should be avoided, drug regulation plays an important role in driving meaningful drug development. A well-functioning regulatory body helps to sustain the markets that reward medically useful innovation. Requiring demonstrations of efficacy and safety before marketing approval creates strong incentives to generate high-quality evidence and helps to ensure that almost all patient exposure to unproven drugs is in the context of well-designed clinical trials.

Several recent policy initiatives have sought to weaken standards for regulatory approval. The REGROW Act proposes to grant a 5-year regulatory approval for somatic stem cell–based interventions based on "preliminary clinical evidence of safety and a reasonable expectation of effectiveness." The 21st Century Cures Act passed by the House of Representatives in July this year (www.congress.gov/bill/114th-congress/house-bill/6/text) offers provisional license for approval of certain new antibiotics in so-called limited populations without conventional clinical trials and gives the Secretary of Health and Human Services the authority to expand this pathway to other drug categories if "the public health would benefit from expansion."

Candidates should declare their views on drug regulation. If they favor maintaining, strengthening, or extending approval standards,

then they can offer policies that might provide special incentives for investment in disappointing areas of clinical translation with high unmet medical need, including antibiotic development or drugs for treating central nervous system diseases. If they advocate more permissive standards, then they should explain how they intend to address the inevitable market failures or how patients might be indemnified for injuries incurred in receiving unproven drugs.

THE MARKETPLACE OF APPROVED PRODUCTS

The postapproval period remains a part of clinical translation—it is when the community should follow up on signals that emerge during the drug development process and when predictions of a drug's promise based on clinical trials are experienced in real-world settings. Despite enhancements in the 2007 U.S. FDA Amendments Act, the FDA still has limited ability to require that postapproval studies be conducted promptly. In addition, the FDA lacks postapproval surveillance resources to aid in the close monitoring of evolving knowledge about drugs or devices (www.nap.edu/catalog/11750/the-future-of-drug-safety-promoting-and-protecting-the-health). As a result, postapproval studies that the FDA requires upon granting approval for a drug may not be started or completed in a timely fashion.

New regulatory programs have emerged that offer brighter prospects. In 2007, Congress authorized the Sentinel program, in which FDA uses the collective resources of 17 national data partners to monitor the safety of approved drugs. Another tool has emerged with Risk Evaluation and Mitigation Strategies (REMS), FDA-mandated programs organized by the drug's manufacturer to provide safeguards for the use of certain high-risk medications, including enhanced certification for prescribing physicians or required registry entry for patients. REMS covered about 10% of drugs approved between 2010 and 2014.

Because of limitations in the FDA's passive and active monitoring systems, manufacturers also provide an essential role in evaluating drug risks and benefits after approval. A U.S. Supreme Court case in 2007 reinforced that brand-name manufacturers bear primary responsibility for keeping their drug label updated. However, the Supreme Court in subsequent cases has interpreted various statutory provisions to exclude generic manufacturers and high-risk device manufacturers from similar responsibilities.

Candidates should offer a vision for how they will ensure that the safety and effectiveness of approved drugs are managed and how the different actors will coordinate to gather the necessary data and communicate updates to physicians and patients. Such visions should include how to ensure that the Sentinel program fulfills its potential, whether additional programs like REMS are needed, and what changes in the law are needed to fill in the gaps in oversight left by the recent Supreme Court decisions. One key upcoming date will be whether the Patient-Centered Outcomes Research Institute (PCORI) will be renewed in 2019. Initially intended to evaluate comparative effectiveness and safety for approved therapeutics, its mandate was changed by last-minute political maneuvering to a focus on decision aids and other tools for improving patient decision-making. PCORI would be a natural center for many of these activities, but this would require an expanded mandate and another substantial commitment of funding.

CONCLUSION

Unlocking the therapeutic value of basic science demands the sustained collaboration of many different actors, including industry, regulators,

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scientists, funding bodies, and patients. Each enters this collaboration pursuing different personal goals. Laws, regulations, funding, and oversight help to secure the terms of cooperation among these various actors and are key to fostering clinical translation and directing it toward the most pressing medical and public health needs.

Each point on the continuum from basic science to medical practice is sensitive to incentives, funding opportunities, and regulations that are shaped by federal policy. Candidates should signal to patients, their families, private drug developers, and the research community how they intend to negotiate these and other critical issues.

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