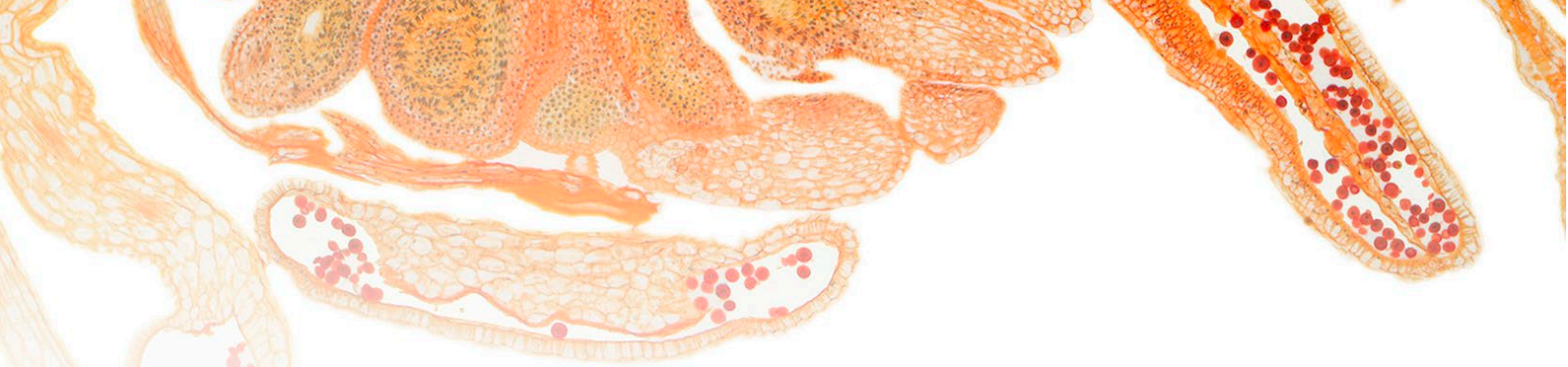

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POLICY FORUM: PEER-REVIEWED ARTICLE

What Should Be Roles of Industry and the Public in Diagnostic Research?

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Abstract

Despite legislative attention from Congress in the 1980s, diagnostic research on rare diseases is not lucrative enough to garner sufficient private funding. The Undiagnosed Diseases Network supports diagnostic research and intervention innovation for patients with undiagnosed or rare conditions. This article considers structural conflict endemic among values seen as promoting corporate fiscal policy (eg, investment return, market share dominance) and values traditionally seen as motivating good public health policy (eg, rescue, non-abandonment). It argues that taxpayer investment in pharmaceutical innovation should be protected by expanding public understanding of conflicts of interest.

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Incentivizing US Drug Development

Even though markets can be shaped to produce common good, current drug development policy heavily supports public investments in private companies, making companies with high profit margins rich but restricting access to government-subsidized, privately produced drugs.[1] Limited access to pharmaceuticals is especially true of those with rare diseases, both undiagnosed and misdiagnosed, for whom the basic knowledge of etiology and resources necessary for diagnosis are not being produced. Profit-making values are infused into pharmaceutical companies, research funding priorities, and regulatory policy, leaving groups whose health issues do not accord these values undiagnosed and untreated in significant numbers. It is therefore important to accurately assess the degree to which public resources may be unfairly subsidizing commercial entities.

Other institutional forms (eg, public benefit corporations) or practices (eg, negotiating licensing agreements that include required access) could be adopted to increase therapeutics' accessibility and affordability.[2] One such effort to sustain academic centers' access to noncommercialized genetically modified cell therapies for rare diseases would use expanded access protocols and also allow for cost recovery.[3] A more far-reaching alternative is to reject the notion that the public sector's role is to fill the gaps created by markets and to require the economy to serve health.[4] This article calls

for equitable accounting of public research contributions for development of rare disease diagnostics and therapies.

Current US Drug Development Policy

The Bayh-Dole Act (BDA) of 1980 empowers universities, nonprofits, research institutes, and businesses to own and commercialize inventions funded by federal programs.[5] Yet the BDA could be said to be insufficiently protective of taxpayers' interests for several reasons. First, it focuses on applied research rather than on the largely publicly financed basic research necessary for downstream study and product development.[5] In addition, government research support is underreported in patents,[6] including those related to diagnostics, thereby limiting potential public health and safety benefits. And, more generally, a recent review concludes that measures to link public investment to pharmaceutical prices (eg, through Medicare price negotiations) have been implemented without accurate, transparent tracking of government pharmaceutical investment and with little effective oversight[7] and thus do not effectively incentivize diagnostic research for rare disease.

The Orphan Drug Act (ODA), now 42 years old, has been helpful but insufficient in incentivizing the development of drugs for many rare diseases, which the ODA generally defines as those affecting fewer than 200 000 Americans or more than 200 000 Americans if the cost of developing a drug for the disease cannot be expected to be recouped from US sales of the drug.[8] The reason for this failure is that the ODA includes incentives beneficial to sponsors who develop drugs for rare diseases that are also approved for more common conditions and could be developed without ODA incentives.[8] One could conclude that the ODA has been "gamed" and should be rewritten to assure that it actually supports rare disease research.

Pension and state funds also support biomedical research and development. While investors of this money have a fiduciary responsibility to act in the best interests of the savers, ironically, the diagnostics and therapeutics so produced might not be available to them because of cost.[9]

What work is being done to ameliorate this distortion of incentives? Few alternative structures have been tried and tested. Against this policy background, patients, clinician-investigators, and institutions supporting their work in the undiagnosed disease space face greater quality-of-care and ethical risks, in part because current policy is insufficiently protective of the public's investment. However, a recent National Academies of Sciences, Engineering, and Medicine report has considered regulatory improvements to advance rare disease diagnosis and treatment, including allowing many kinds of available data collected outside of randomized clinical trials— such as natural history data, registry data, real-world evidence, patient-reported outcomes, and data from open label extension studies—to be "used as supplementary, alternative and/or confirmatory evidence in support of regulatory submission and review of a drug product."[10] The report also cites an ethical obligation for the US Food and Drug Administration to share relevant information on the review and approval of drugs and diagnostics to treat rare diseases.[10]

Alternatives

Alternative approaches to incentivizing rare drug development that support public values and address issues of justice are available. A view from business ethics is that structural problems, including those affecting health, require collective and collaborative

approaches to ameliorate. Corporate legitimacy thus must increasingly be conceptualized as requiring collective effort in working toward resolution of structural problems, no matter who caused them, with the understanding that individuals face limitations in correcting the problem. On this view, profits are an instrument to fulfill corporate purpose rather than the actual purpose itself.[11] More in the public realm is the United Nations Convention on the Rights of the Child, adopted in 1989.[12] Since many rare and undiagnosed diseases occur in children, rights addressed or implied in this document—the right to advocacy and support, the right to health care, and the right to global effort to realize the goal of upholding children's rights[12]—are relevant to incentivizing rare drug development.

Broader frameworks with patient-centric values can also provide perspective on overcoming structural problems that impede access to new drugs. The Responsible Research and Innovation framework differs from current practice in considering societal engagement in research and innovation to be an early, permanent, and continuous endeavor as a means of ensuring that innovation processes are aligned with fundamental societal values.[13] Especially important is framing of the issue at stake by moving away from the neoliberal perspective of innovation and growth as the end good in itself toward consideration of broader impacts and values.[13]

Recent extensions of the concept of conflict of interest (COI) are also helpful in protecting public investment in drug development. Recall that a widely accepted definition of COI was first summarized for the medical community in 1993 as "a set of conditions in which professional judgment concerning a primary interest (such as a patient's welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain)."[14] COI has primarily been applied to individuals with financial interests. Public-private partnerships, widely championed by governments to further economic goals, risk the public partner's interests through the private partner's institutional conflict of interest, such as when basic science contributions of the public partner are not adequately acknowledged.[15] Also relevant is the newly defined concept of structural conflict of interest—a set of conditions in which the primary interest of one sector (eg, health) is unduly influenced by the interests of another sector (eg, commercial) with different and often conflicting values.[15] Mitigating structural COIs requires policy revision that protects public interests,[15] such as by amending the BDA to better acknowledge contributions of publicly funded basic research.

How have these institutional and structural COIs been addressed? In the mid-1990s, demand for access to HIV therapies led pharmaceutical companies and their trade group to begin to attend to questions of access. A few initiated opening access to their already-approved products through philanthropic or other programs.[16] Importantly, the response to public pressure did not appear to extend to developing diagnostics and therapies and keeping them available for diseases that would not eventually be profitable. Why might that be the case? Sparke and Williams suggest that the power of pharmaceutical companies during the COVID-19 pandemic arose from structural cartelization among the companies and state authorities, which privilege economic growth, and philanthropies, which amassed their resources through pursuit of these same values.[17] Sparke and Williams label this situation as collusion, with nested, overlapping, and deeply networked relationships that enforce monopoly power. States invest in the basic and applied science that is freely available to firms and that reduces the risks of corporate product development[17] without consideration of public health

values. One could conclude that these structural issues are reflected in the public policies reviewed above, which have largely failed to protect the public investment in rare disease diagnostics and treatments.

Improving Diagnostic Research

Since most pharmaceutical research and development relies heavily on fundamental research from the knowledge commons, recalibration of benefits to better favor public interest seems justified. In a step in that direction, Modi and colleagues note that American and European pharmaceutical manufacturers and industries have made a commitment to share participant-level data and study-level data and protocols from clinical trials, provide public access to clinical study reports, establish public web pages displaying company data sharing policies, and publish results of all phase 3 clinical trials.[18] While "no US or EU [European Union] regulations currently mandate participant-level data sharing from industry-sponsored medicine trials,"[18] the companies should be pressed to uphold this agreed-upon commitment.

For undiagnosed diseases networks, there is an important obligation to construct a specialized infrastructure that includes standard definitions, data codes for medical records, network access to expert clinicians, evidence-based clinical practice guidelines, and globally coordinated diagnosis and research infrastructure so as to optimize access to clinical trials, prevent ineffective treatment, and take advantage of therapeutic windows. While artificial intelligence and digital tools to consistently reevaluate undiagnosed disease are under development,[19,20,21] the paucity of economic evaluations of rare disease diagnosis and treatment, including of cost-of-illness burden for patients and families, is unacceptable because it obscures real risks to patients and families.[22] Because rare diseases are geographically dispersed, the Undiagnosed Diseases Network International—a partnership among clinicians, researchers, and patient organizations—which launched in 2014 to help fill gaps impeding diagnosis for rare diseases,[23] is in a strong position to address the inequities addressed in this commentary.

Finally, bioethics literature highlights the necessity of self-advocacy to access clinical diagnosis and care and motivate public interest in advancing research relating to rare conditions. However, there is inequity among rare disease groups' self-advocacy capacity, as some do not have the educational, financial, or social resources to move their cause forward.[24] In part, this unjust situation reflects a poorly coordinated approach to rare disease at the federal level and failure of the health care system to provide opportunity for persons with rare diseases to participate in agenda-priority setting. Such a situation increases risks, reduces quality, and increases costs of care, as well as presenting ethical challenges for patients, families, clinicians, investigators, and the institutions in which care is provided and research produced. Petrov[25] has noted that every health care system must weigh rescue and non-abandonment for sick persons against using resources to promote population welfare. Although no one normative moral theory settles the conflict and societies vary in their views of an appropriate balance,[25] health systems must address it.

Conclusion

Current US policy does not protect public investment in research that should benefit persons with diseases that are not profitable. Regulatory frameworks could be amended to properly recognize the contribution of publicly funded basic research. Several value frameworks urge stronger patient involvement in priority setting and access to

resources. Because rare diseases occur around the world, research and clinical services must be global, supported by an infrastructure of data and expertise. Effective and safe diagnosis and treatment, free of stigmatization and disbelief, should be available for these patients—irrespective of their condition's rarity. Lack of interest or investment[26] is not acceptable. Ng et al state: "[W]hile no country has effectively addressed the challenge of financing rare diseases, the majority have clearly acknowledged that fairness of access is a moral obligation of public health systems."[27]

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