21st Century Cures Act: An Act of Cure or Diagnosis?

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THE 21ST CENTURY CURES ACT¹ is a positive step for biomedical innovation. However, despite a rare bipartisan approval in the House of Representatives with an overwhelming vote of 344–77, public opinion is divided; naysayers have already vocally claimed that the reforms do not go far enough, while others have criticized the bill for promoting increased approval speeds at the expense of patient safety.² As biomedical researchers and patients wanting novel, and safe, therapies to reach the market, it is difficult not to sympathize with negative factions; but is this fair or productive?

Health care translation, defined in the 21st Century Cures Act by the trinity of discovery, development, and delivery, is by nature a complex and fragmented process. As such, the success of the legislation should be judged not by its immediate impact in overcoming entrenched regulatory and research practices, but rather by its long-term impact as a foundation for sustained improvements in the efficiency and rate of life science translation. The legislation is a welcome public acknowledgement of what many health care payers and biomedical researchers have effused for some time: Our current funding and regulatory infrastructure for novel therapeutics and devices is inadequate. We are nearing—some would argue deep within—a health care crisis.

To offer a dose of perspective and to mitigate the cognitive bias shared by writers and readers engaged in biomedical innovation, the use of legislation as a point of crisis diagnosis and potentially cure is not new. Almost 800 years to the day since the 21st Century Cures Act was passed through the House of Representatives, when the greatest health care threat was the bubonic plague, the Magna Carta was drafted to acknowledge major injustices in the contemporary legal system. This medieval charter did not re-

solve England's political tensions overnight; rather it was repealed and reenacted in multiple guises over centuries to come. But it did establish now respected boundaries between the State and its people. In other words, the State could not be a passive participant in peoples' liberty. Analogously, through the 21st Century Cures Act, the federal government cannot be a passive participant in health care translation and improvements in patient outcomes.

A cornerstone of the Magna Carta was the protection of Church rights, namely managing the delicate relationship between Church and State. During the 13th century, the Church was seeking relative financial and political autonomy from the state, despite being remotely managed from Rome. Locally, regional leaders required the support of the Church as a major landowner and influencer of public opinion. The corollary in 21st century science is the delicate balance between the government as the major funder of basic research (and payer for commercialized products and services) and the academic research community seeking intellectual autonomy and by proxy pseudo-control over the allocation of state resources.

The 21st Century Cures Act makes sensible, and in some cases unprecedented, provisions for the support of “[inherently] high risk, [research that has] the potential to lead to breakthroughs” [The 21st Century Cures Act, Sec. 1028]. Previously, this has been the unspoken remit of disease-specific foundations and novel academic industry “translational centers.” This is complemented by support for encouraging “young and emerging scientists [Sec. 1041 and 1042],” principally, by a loan repayment program. The potential contribution of these measures to accelerating life science translation is unclear. The disparity between remuneration in academic and industrial careers is a significant

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factor in many early career scientists leaving day-to-day research, during a period where they are actually at their most innovative.³ As such, loan repayment support is likely to have swift and direct impact on retention. Nevertheless, fundamental issues characterizing the extraordinarily poor diversity and inclusion profiles of academic institutions, such as ageism, must be addressed substantively to encourage the brightest young minds to pursue academic careers. These issues are self-perpetuated in the principle of peer review.

Peer review is amongst the most sacred of cornerstones of academia; however, in what other sector does one allow the perceived novelty of high-risk and high-impact research to be assessed by committees that are not purposely composed to ensure balanced decision making? It has been convincingly argued that in many situations homogeneous groups in fact make worse decisions than diverse groups, even if diverse groups are of varying IQ.⁴ While it is imperative that peer review committees are not dominated by “mavericks,” it is essential that they do become more diverse and inclusive—age, academic disciplines, industrialists, patient groups, regulators, and payers. The step change promised by “high-risk” research will not be realized unless those charged with allocating funds are willing to take risks.

Set against the backdrop of a monarch threatened by overly powerful nobility, the Magna Carta made provision for illegal imprisonment. The analogy in the 21st Century Cures Act is obvious—unjustly restricting the development of novel therapeutics and devices due to archaic regulatory procedures and a failure to adopt the latest technology appraisal methodologies, while safeguarding patient safety, in so far as possible.

Risk-to-benefit appraisal has been an en vogue term in regulatory science for many years, yet arguably its direct impact on patient safety and accelerating drug development has been constrained by a failure by regulators to insist on its formal inclusion and publication in regulatory submissions. This is complicated in part by the desire to ensure the confidentiality of patient and commercially sensitive data, while presenting any analyses in a standardized form that is accessible to a diverse audience, including patients. Combined with provisions for the use of novel biomarkers and surrogate end points, along with advances in “Big Data analytics,” risk-to-benefit appraisal has the potential to be amongst the most transformative inclusions in the 21st Century Cures Act [Sec. 2001].

Future entanglement in negotiations around data confidentiality are unavoidable—and if pragmatic, wholly justified. However, throughout, please reflect on the injustice to patients and precious research resources perpetuated by re-testing the same failed therapeutic candidates on patients for reasons of perceived confidentiality.

The apotheosis of improved health care risk management tools are adaptive clinical trial designs (European Union, Adaptive Pathways; United States, Breakthrough Status, Fast Track Accelerated Approval), permitting accelerated access for the most promising candidates for high-unmet medical needs, subject to enhanced pharmacovigilance. Similar principles are embodied in the Magna Carta’s commitment to “swift justice.” In health care, “justice” is multi-factorial, embodying the viewpoints and needs of basic researchers, patients, and a fair risk adjusted return on investment for commercial partners. One issue not explicitly considered in the 21st Century Act is the need for a return on the public sector’s support of high-risk biomedical research.

A major innovation in the Magna Carta was a limitation on exorbitant payments to the Crown. Conversely, a weakness of the 21st Century Cures Act is a failure to explicitly secure a reasonable return on investment for funders of innovation, such as the National Institutes of Health Innovation Fund [Sec. 1002], in a manner that does not discourage spin-out formation or burden pre-profit start-ups with high licensing fees. For example, the Cystic Fibrosis Foundation’s (CFF) initial support of the drug Kalydeco included a modest claim to any future revenue generated by the research.⁵ Today, the securitized licensing revenue arising from Kalydeco has allowed CFF to reinvest upward of \$1 billion into research for tomorrow’s therapeutics. A similar “evergreen” model has been employed by Syncona Partners, the in-house venture capital fund of the Wellcome Trust.

The final parallel is between the Baron Council, appointed to ensure the fair and consistent implementation of the Magna Carta, and novel structures and organizations proposed within the 21st Century Cures Act to ensure that the legislation catalyzes tangible and sustained progress in biomedical research, as well as ensuring prudent deployment of public funds. In the 21st Century Cures Act, these provisions to support implementation fall into two dimensions—industrial and clinical adoption.

Historically, “blue sky” support for scientific innovations has self-selected for basic research likely to generate publications in high-impact journals, neglecting the advances in late-stage applied sciences, including bioprocessing, required to translate therapeutic innovations toward industrial adoption. The 21st Century Cures Act includes provision for investment in research programs pertaining to “continuous drug manufacturing” [Sec. 2161], which, while unlikely to grab headlines in the mainstream press, is a critical strategic investment accelerating time-to-market, lowering cost of goods (COGs), and supporting product developers “locking down” their processes earlier in product development strategies to facilitate access to adaptive clinical trial pathways.

A key pillar of the Act is the establishment of public-private partnership, the “Council for 21st Century Cures” [Sec. 281]. The Council has a remit to promote international collaboration, including specifically with the European Union Innovative Medicines Initiative (IMI) [Sec. 281B]. It prescribes an apt range of members, from academia, the biopharmaceutical industry, and payers to the digital technology industry, thereby acknowledging the criticality of effective collaboration among these protagonists in the translation pathway and the ongoing digitalization and democratization of health care research and development and delivery.

There are, however, some curious omissions from an otherwise holistic Act. Regenerative medicine, encompassing cell therapy, gene therapy, immunotherapy, and tissue engineering, is one such omission; few areas have received as much public interest and investment in recent years. After a number of initial clinical failures, particularly for mesenchymal stem cell (MSC) technologies, regenerative medicine is now yielding some extraordinarily efficacious therapeutics for presently unmet medical needs, for example, the burgeoning field of onco-immunotherapy, including gene-modified T cell receptor (TCR) and chimeric antigen receptor–modified T cell (CAR-T) technologies. Regenerative medicine clinical trials and manufacturing face a number of challenges, including effective implementation of placebo arms in trials⁶ and ensuring

cost-effective and accurate real-time lot release–testing technologies.⁷ The reason these issues are not addressed may be perceived public over-investment in regenerative medicine with limited return to date. While potentially fair, such concerns risk jeopardizing government involvement, and therefore return, at the foot of the regenerative medicine J-curve, which many would argue is now in sight or upon us.

Furthermore, and of critical importance to the innovation process, is intellectual property (IP).^{8,9} Innovations in IP structures have been historically limited in health care, and there is only one IP provision in the 21st Century Cures Act, concerning patent extensions for drugs approved for new indications or rare diseases [Sec. 505G]. A crude analysis would suggest that the three greatest IP innovations in recent years were provisions within Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreements to suspend IP rights in the event of pandemics, patent boxes worldwide, and the Association for Molecular Pathology v. Myriad Genetics case.¹⁰ Although IP is often viewed as a “necessary evil,” when legislated and leveraged appropriately it can accelerate invention, innovation, and translation. This is demonstrated by tremendous advances in open innovation models, exemplified by the case of the drug JQ1,^{11,12} and must be recognized in future health care acts.

Surprisingly, some key challenges associated with the successful development of cures are omitted from the act. Greater availability of cures will inevitably lead to a healthier, but longer-living, population. Socially and economically, the effects of increased healthy human life span will be significant, and regulation needs to address this. Furthermore, while developing cures is extremely important, equally important is incentivizing and establishing acceptable regulatory structures to support *preventative* medicine, which could dramatically reduce health care costs and increase population health. The lack of appreciation of the wider socio-economic impacts that developing cures may have in the future is perhaps symptomatic of a problem in health care, and indeed policy, more generally: The emphasis is on “curing” the problems of today rather than preventing those of the future. Such thinking can be applied at the individual patient level, as well as more broadly to the translational ecosystem and beyond. Long-term impacts of curative and preventative medicine must be considered; reimbursement, for example, is likely to be complex and must be discussed now.

The Magna Carta was drafted to address a pressing contemporary problem—strained relations between the Church, State, and nobility. In so doing, the Charter provided a proxy for the diagnosis of political tensions and the threat they posed to justice. The 21st Century Cures Act is exactly the same, a very public diagnosis of unacceptable provision for health care translation, set against the backdrop in spiraling unmet health care needs and unaffordable health care costs. Neither the problems of Church and State nor those of the entire ecosystem for health care translation can be “cured” overnight through a single act of government. And those spectators who have derided the Act as a failure because it has not and is unlikely to achieve this are short sighted and actually doing a disservice to those of us committed to health care translation.

Today’s 21st Century Care Act, under the right stewardship may be a transformative platform for achieving to-

morrow’s health care outcomes, not a health care revolution in itself but potentially an essential catalyst for one. In the same manner, the Magna Carta catalyzed a revolution in global legal systems, including the United States. Therefore, the most erudite prospective analysis of the 21st Century Care Act may have been offered almost 50 years ago, against the backdrop of an altogether different “revolution,” by the Rolling Stones: “You can’t always get what you want; but you might just get what you need.” Many may “want” an overnight solution to our shared frustrations at the rate of health care translation. However, criticizing policy makers and politicians, many of whom do not have a scientific or health care background but who voted across political lines to support the 21st Century Care Act, does not benefit anyone.

Our greatest “need” may have actually been for a statutory basis to assess and mitigate multi-factorial systemic risks and benefits more objectively—something the Magna Carta and the 21st Century Care Act both provide. It is up to today’s global health care translation community to nurture this for future generations of researchers and patients.

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