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Peer Commentary

Precision medicine: a matter of regulation or collaboration?

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Clearly laying out the multiplicity of existing regulatory instruments that could serve to frame the future of precision medicine, the five key 'ingredients' listed in the conclusion of Nicol et al., create a recipe that may well ensure the success of such a framing exercise:[1]

(i) appropriate consideration of safety, efficacy, and patient need;
(ii) cost effectiveness;
(iii) consistency/equivalency across geographical, technological, and institutional borders;
(iv) respect for cultural differences; and
(v) genuine engagement with all relevant stakeholders.

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1 Diane Nicol et al., *Precision Medicine: Drowning in a Regulatory Soup*?, 3 J. L. & BIOSCI. 281, 303 (2016). [hereinafter Nicol]

Whatever the future regulatory recipe for precision medicine, they rightly conclude that 'the sector needs to remain adaptive, flexible, and responsive'.[2]

A few comments however, on some of the suggestions made as to the possible correct measurements for future regulatory slicing and dicing. According to the strategy for the USA's Precision Medicine Initiative (PMI) for example, it envisions the recruitment of a longitudinal cohort of one million participants.[3] The cohort has to be diverse and representative cutting through all strata of society and encompass asymptomatic, healthy individuals, not just patients.

A cohort approach follows individuals over time across a series of environments and contexts so as to capture the interactive effect of the latter on human health and resistance to disease—a form of infrastructure science.[4] Such a large interoperable dataset representative of modern human diversity and behaviors allows for subsequent stratification into sub-populations for targeted, resource allocation efforts that include prevention and possible treatment (eg pharmacogenomics).[5] In this way, the next, medical care step offered to individuals and their families can be sufficiently precise and personal to meet the professional standard of care.

Consent to be a member of a longitudinal cohort means participating in a population project with a standardized set of core measurements and questionnaires (ie variables) that must be consistently applied in order to achieve statistical quality and significance.[6] Such cohorts require ongoing updates, sampling, measurements, and linkage to medical records and other databases under a broad consent that is a consent that is material and specific to the very epidemiological nature of this form of scientific endeavor. Yet looking back over a decade at the acceptability of national, longitudinal cohorts that include medical, genomic and environmental data with possible future access, and use by others including the commercial sector, the broad consent approach was not without its detractors, though the proposed Common Rule supports it as does the PMI.[7] Ongoing governance and oversight of a cohort is a *sine qua non* to maintaining the confidence and trust of broadly consented participants. It should be noted that even the broad consent of cohort studies usually contains 'dynamic' additional choices and options that could be termed as the three 'Rs' of research.

The first is the ongoing right to withdraw at any time—a right inherent to all ethical, biomedical research. The second is the right to be asked for permission upon recruitment for further re-contact concerning additional studies internal to the cohort or coming from outside researchers. If permission to re-contact is refused upon recruitment, this implies no further internal or external contact but participants can agree to continuation of passive follow-up on the core elements of the cohort. Were potential participants to refuse at recruitment even such longitudinal passive linkage, they would

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2 *Id.* at 298.

3 The White House, FACT SHEET: President Obama's Precision Medicine Initiative (2016), https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative.

4 Paul N. Schofield et al., *Sustaining the Data and Bioresource Commons*, 330 Science 592 (2010).

5 Bartha Maria Knoppers, *Genomics: from Persons to Populations and Back Again*, 56 Genomics 237 (2013).

6 Isabel Fortier et al., *Maelstrom Research Guidelines for Rigorous Retrospective data Harmonization*, Int'l J. Epdemiology (2016).

7 Kathy L. Hudson & Francis S. Collins, *Bringing the Common Rule into the 21st Century*, 373 New. Engl. J. Med. 2293 (2015).

probably not be part of a cohort as its very nature requires some form of follow-up of participants over time. This speaks to the collaborative 'resource-building' nature of longitudinal cohorts.

The third 'R' is that of return of results. The last decade of modern, longitudinal cohorts that include biobanking illustrates the prevalence amongst major national biobanks of a 'no-return' approach.[8] The logic of this resides in the realistic need to build such infrastructures alongside and as a foundation for discovery science. Cohort studies and accompanying biobanks cannot promise immediate direct personal benefit in the building of public population reference databases for the future benefit of all citizens.

Today, as researchers with more clinical projects seek to access such classical biobank cohorts with studies applying MRI's, whole genome sequencing and pharmacogenomic tests, the no return policy may well be further challenged as concerns responsibility for clinically significant findings and all the more so, considering proposed ongoing linkage to electronic, medical records. Thus, while broad consent remains a staple ingredient, the third 'R' will increasingly provide dynamic options for the return of certain findings if desired. It should be remembered that the last decade of classical cohort studies all provided feedback at initial assessment and remain in contact with their participants via newsletters, returning general results and re-contacting participants for additional questionnaires thus keeping communication and options 'alive'.[9]

As recognized by Nicol et al., the 'regulatory soup' of precision medicine is also facing other systemic changes as private–public partnerships are encouraged by funders (eg Genomics England). The growing value of data sharing and of Big Data beckons change at all levels of funding and oversight. Particularly, it highlights the need for multi-jurisdictional data sharing to say nothing of mutual recognition in research ethics review procedures,[10] interoperability and oversight mechanisms. Moreover, today with precision medicine, clinicians are becoming biobankers for research, thereby finding themselves in a world of ethics 'research rules' well beyond their professional codes of clinical conduct. Will the ethos of sharing of samples and data environment spawned by the Human Genome Project and today exemplified by the Global Alliance for Genomics & Health (genomicsandhealth.org/) and clinical trial data sharing efforts such as 'clinicalstudydatarequest' (with 13 sponsors), spill over into the clinical domain? Or, are clinicians still in the 'my patient, my samples, my medical records' sphere? Irrespective, patient empowerment and engagement— 'citizen science'— will be the force that changes this mentality as direct-to-consumer (DTC) initiatives as well as clinical trials lend themselves to more dynamic approaches aimed at treating participants as partners. Moreover, combining the soft law and the public educative tools of 'Choosing Wisely' and 'Too Much Medicine' campaigns may well serve to clarify the alleged regulatory soup and typify broader societal approaches.

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[8] Bartha Maria Knoppers, Ma'n H. Zawati & Karine Sénécal, *Return of Genetic Testing Results in the Era of Whole - Genome Sequencing*, 16 Nat. Rev. Genet. 553 (2015).

[9] Bartha Maria Knoppers, Ma'n H. Zawati & Emily Kirby, *Sampling Populations of Humans Across the World: ELSI Issues*, 13 Annu. Rev. Genomics Hum. Genet 395 (2012).

[10] Edward S. Dove et al., *Ethics Review for International Data - Intensive Research*, 351 Science 1399 (2016).

Finally, one should note that the strong points of their analysis on how to channel the regulation of precision medicine include drawing our attention to

- the blurring between the policy boundaries of the clinical and research settings,
- the need to put patients at the centre of health policy,
- the continued utility and applicability of high level 'policy-principled' instruments,
- the wide array of applicable legislation from different sources, and
- the absence of robust evidence of documented harms in the current mix of levels of regulation and oversight.

In this network of regulatory 'ingredients', the authors rightly conclude that 'highly targeted laws' are not the answer. Thus, appropriate governance, and proof of safety, efficacy, and of analytical validity, clinical validity and clinical utility will form the basis of the adoption and inclusion of reimbursed tests, the final arbiter of quality. Irrespective, as stated by the authors: 'The question is not how to regulate but how to regulate well.'[11]

In 2015, Isaac Kohane addressed the 10 major but surmountable hurdles to precision medicine in the United States: linkage, accuracy, blurred boundaries, popular support, Omics writ large, perpetual updating, computation, affordability, representation, and education.[12] To this astute and insightful list, I would add 'think populations'.[13] To meet the socio-political challenges of precision medicine requires a seismic shift so as to build the necessary medical information commons, that is, multidisciplinary, scientific infrastructures that undergird the success of cohorts with the promise of sub-population stratification leading to precision medicine for individuals and families. Thus, the number one challenge is: How to foster the 'common good' via more health data sharing so as to finally achieve quality, precise personal medical care? Collaboration in the building of precision medicine cohorts rests on the willingness to create an infrastructure, population reference databases for better science for everyone, perhaps leading one day to better medicine for 'me'.

[11] Nicol, *supra* note 1 at 301.
[12] Isaac S. Kohane, *Ten Things We Have to Do to Achieve Precision Medicine, 349* SCIENCE *38* (2015).
[13] Muin J. Khoury & Sandro Galea, *Will Precision Medicine Improve Population Health?* JAMA (2016).