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Are We Asking the Right Ethics Questions on Drug Shortages? Suggestions for a Global and Anticipatory Ethics Framework

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> If bioethics is to address the broad range of ethical issues raised by public health policy, including targeted interventions, effectively it must place discussions of choice, consent and autonomy in the context of a wider range of ethical issues. (Onora O'Neill 2011, Nuffield Council on Bioethics, 20th Anniversary Lecture, Cambridge, United Kingdom)

In the *AJOB* target article, Rosoff (2012) presents ethics frameworks to ration drugs and outlines an allocation policy for drug shortages in the United States. While the proposed policy has internal validity, it requires an additional global health dimension to accommodate the reality of interdependencies between developed and developing countries in the supply and demand of medicines. The aim of our article is to address this facet by examining the ethical, legal, and social issues (ELSIs) on medicines in a globally framed, context-emergent, and anticipatory manner. We underscore that many of the global ELSIs on drug shortages are directly emergent from the *actual* context of postgenomics health care. One such global context is the concept of essential medicines, which was not broached in the target article. As part of our discussion on global ELSIs and public health ethics, we note that medicines increasingly will be used together with diagnostics (e.g., genetic tests) as we move toward personalized medicine and theragnostics (i.e., the fusion of therapeutics and diagnostics). Such a "theragnostic" approach (Ozdemir et al. 2009) may become highly valuable and relevant in the allocation of scarce pharmaceuticals. Hence, medicine shortages can also conceivably result from a limited supply of essential diagnostics that may require co-prescription with medicines. We conclude that theragnostics is well suited to apply anticipatory ethics. As a concept, anticipatory ethics can help broaden 21st-century bioethics frames toward global ELSIs (O'Neill, 2011) by providing prospective and real-time responses to highly dynamic, ever-changing, and increasingly globalized realms of postgenomics science, technology, and health care.

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NEED TO THINK BEYOND BORDERS: MAKING THE ELSIs ON DRUG SHORTAGES GLOBAL AND CONTEXT-EMERGENT

Periodic or long-term shortages of drugs are commonplace in both developed and developing countries. This creates complex global interdependencies across nation-states, reflecting in large part the frequent involvement of multiple countries in the research, development, manufacturing, and distribution of pharmaceutical products. Developing nations can contribute to policy innovations for access to essential medicines and manufacturing of health products (Dhere et al. 2011) that impact public health globally. The traditional Westphalian model of independent sovereign nation-states, therefore, does not adequately recognize the interdependencies in global governance for health (Kickbusch 2011) that instrumentally shape supply, demand, and access to medicines. For drug allocation policies to be sustainable within each nation, the ELSI frames need to be global and attuned to a broad range of human values and ethical principles. For example, while the principle of individual autonomy has historically prevailed in bioethics frameworks post Nuremberg—particularly in the Western developed countries—other ethical values inspired in part from the public health context, such as solidarity and citizenship, are emerging (Knoppers and Chadwick 2005; Lunshof 2008; Ozdemir 2010; Ozdemir et al. 2011). In order to map the global ELSIs on medicine supply, demand, and rationing, such broad diversity in values and ethics norms must be recognized.

In addition to broadening the existing bioethics frames to align with global health, a comprehensive vision of "global ELSIs" requires a second tenet: validation of the global ELSI maps in the actual setting and realities of global health practice. A case in point is the concept of "essential medicines," which was unexamined in Rosoff's target article. As defined by the World Health Organization (WHO), essential medicines are "medicines that satisfy the priority health care needs of a population. They are selected with regard to disease prevalence, evidence of efficacy, safety, and comparative cost-effectiveness. Essential medicines are intended to be available in functioning health systems at all times in adequate amounts, in appropriate dosage forms, with assured quality, and at prices individuals and the community can afford" (WHO 2011).

The concept of essential medicines is directly pertinent to understanding and responding to the ELSIs associated with drug shortages. For example, in an empirical study of the U.S. State Medicaid Preferred Drug Lists (PDLs) and their concordance with the WHO 16th Essential Medicines List (EML), only 6 of 120 EML medicines appeared on fewer than 50% of PDLs (Millar et al. 2011). More importantly, PDL-only medicines ($n = 249$) were less likely than were EML medicines ($n = 120$) to have generic versions available (56% vs. 76%) and to be first-line treatments (21% vs. 41%) (Millar et al. 2011). These recent observations strongly support the idea that a shortage of essential medicines, given their generic availability and greater likelihood of being a first-line treatment, can have far more serious population health consequences than medicines that are not in the EML. While Rosoff's proposed approach is "fair, equitable, and reproducible," we propose the essential medicines framework for consideration precisely in order to optimize the use of this particular, well-validated subset of medicines that attests to the global needs for drug availability. Bringing the concept of essential medicines to the fore in the event of medicine shortages facilitates the development of informative ELSI analyses that reflect the actual needs of both local and global health.

To the extent that ELSIs emerge from the dynamic context and realities of health care, science, and technology, it is noteworthy that diagnostic test access can have a direct impact on the allocation of medicines in public health services. Pharmacogenomics and other novel tests are gradually being introduced as companion diagnostics for personalized health care to rationally select dose and type of medicines that can otherwise be toxic or ineffective (Ozdemir 2010). For optimal public health, we will eventually need equitable access to both medicines and diagnostics. As a practical way forward, we propose that the creation of an essential diagnostics model list may help ensure a steady and equitable global supply of both essential medicines and essential diagnostics.

A CALL FOR ESSENTIAL DIAGNOSTICS MODEL LIST

In our proposed broadened frame of global ELSIs, an "essential diagnostics model list" would serve as a welcome salient strategy to catalogue field-tested diagnostics and develop targeted health interventions in global public health (Ozdemir et al. 2009). This model list would need to overcome certain operational hurdles (e.g., heterogeneous human diseases and regional capacities) and orient itself in a collective manner so as to better align market mechanisms with socially adequate solutions (Khoury 2009). Nonetheless, an evidence-based policy innovation such as an essential diagnostics model list, which is based on the precepts of public health and equal access, would offer affordable and equitable access to diagnostics, especially in resource-limited settings. It would also accelerate the transition of novel diagnostics (e.g., genomics, proteomics, metabolomics) into primary health care, an area we consider particularly vital as the world begins to confront the realities of postgenomics health care and personalized therapeutics.

An essential diagnostics model list would furthermore necessarily reflect the increasingly connected steps of diagnosis and treatment (i.e., theragnostics). Rosoff effectively describes the current reality: Class A evidence-based information for many medicines is either lacking or incomplete. We propose that pharmacogenomics tests included in an essential diagnostics model list should meet the Centers for Disease Control and Prevention (CDC) ACCE evidentiary framework, which invokes key criteria for evaluating DNA (and related) diagnostic tests. These criteria are: (A) analytical validity (how accurately and reliably the test mea-

sures the genotype of interest); (C) clinical validity (how consistently and accurately the test detects or predicts the intermediate or final outcomes of interest); (C) clinical utility (how likely the test is to significantly improve patient outcomes); and finally, (E) ethical, legal, and social implications that may arise in the context of using the test (Zimmern 2009).

To the extent that there is committed international investment in personalized medicine, an essential diagnostics model list can well be considered a crucial aspect of the global ELSI agenda in the near future as it reflects an anticipatory policy measure that prevents missed opportunities to identify worthy diagnostics in public health, as well as preventing premature translation of diagnostic candidates.

CONCLUDING REMARKS: TOWARD ANTICIPATORY ETHICS?

For the avid reader, it might perhaps come across as a surprise that a long-standing and existing practice in medical therapeutics such as essential medicines or the reality of global interdependencies among developed and developing countries is not addressed in the medicine allocation policy proposed in Rosoff's article. We propose that such "anticipatory ethics" would foster more nuanced and panoptic bioethics policy responses to emerging global ELSIs. Anticipatory ethics builds on the idea that through closer engagement with science, technology, and their materiality, bioethics can achieve two primary gains. First, it will lay a foundation for anticipation and early recognition of the emerging ELSIs from their outset. This seems more than essential to the extent that global ELSIs emerge from the highly dynamic context of global health and the technologies embedded in its practice. As suggested by O'Neill (2011), there is a broader range of bioethics issues emergent from global public health. Second, closer epistemic proximity and exchanges between bioethics and science would allow real-time and prospective policy responses to the emergent global ELSIs. However, a closer engagement between bioethics and science also calls for measures to maintain the independence of bioethics so that it is not co-opted by its subject matter. For 21st-century global ELSIs and public health ethics to respond to the challenges of global health, anticipatory ethics warrants further recognition to move bioethics from its traditional enabler function to one that is instrumental and actively shapes the science, health care, and innovation trajectory. ■

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