Darwin meets Mendel in the reproductive medicine field: *Homo sapiens* 2.0 is inevitable

Reproductive Endocrinology and Infertility (REI) was officially recognized as a subspecialty in the United States in 1972. The first US baby born as a result of in vitro fertilization dates back to 1981. Since then, the field of reproductive medicine has witnessed dramatic medical and technological advances. Our relatively new subspecialty accounts for more than 8 million births, a drop in the ocean of the 7,625 million worldwide, but our field has just started.

The genomics revolution has transformed not only medicine but also plant and animal worlds. Most importantly, it will transform the history of humankind through the entry point of REI, specifically through the preconceptional space, because now the human genetic code as well as the code of all living organisms is readable, writable, and hackable (1).

Preimplantation genetic testing of embryos for monogenic diseases (PGT-M) was the first diagnostic genetic application in reproductive medicine based on the readability of the human code. It was developed to prevent Mendelian single-gene defects (autosomal or X-linked dominant/recessive), severe childhood lethality or early-onset disease, cancer predisposition, and human leukocyte antigen typing for histocompatible cord-blood stem cells transplantation. The field soon moved to the identification and selection of euploid embryos by analyzing all 23 pairs of chromosomes via PGT for aneuploidy (PGT-A). The latter analysis is routinely performed using deoxyribonucleic acid (DNA) obtained from 4–8 cells of the trophectoderm layer and now even cell-free embryonic DNA present in blastocyst-conditioned media. PGT-A currently leverages next-generation sequencing technology to uncover meiotic and mitotic aneuploidy affecting whole chromosomes, as well as duplications/deletions of small chromosomal regions. However, the interpretation of mosaicism is an example of the technology getting out in front of us. The resulting uncertainty about what embryos should be transferred serves to erode patient trust as well. A step forward was the use of structural chromosome rearrangements (PGT-SR) to identify Robertsonian and reciprocal translocations, inversions, and balanced versus unbalanced rearrangements (up to 6 Mb). The ultimate frontier is likely to entail PGT for risk prediction of polygenic diseases (PGT-P). This technique takes us from reading simple letters (As, Cs, Ts, and Gs) to writing complex stories (i.e., evolving to multifactorial, polygenic risk prediction). Common multifactorial diseases such as diabetes mellitus, coronary heart disease, and cancer are caused by a combination of genetic, environmental, and lifestyle risk factors; preliminary risk scores are now being generated to predict the future risk of complex, adult-onset diseases in a cohort of embryos. It follows that current clinical practice allows physicians and patients to select through different PGT applications a potentially healthier embryo for transfer, but some may try to open the door for broader embryo selection criteria such as intelligence, environmental resistance, etc. The technology will continue to progress allowing for embryo selection based on nonmedical traits.

The genetic code is writable. Scientists have created a living organism whose DNA is entirely human-made. In 2016, a team of scientists from the Venter Institute built the genome of a bacterium from scratch and incorporated it into a cell to create what amounted to the world's first synthetic life form (2). Since then, colonies of *Escherichia coli*, the DNA of which was constructed from scratch by humans, have been engineered to churn out biofuels, soak up carbon dioxide from the atmosphere, and even manufacture vaccines as we have learned during the pandemic with the Pfizer vaccine. Although human nature is capable of innovating for the good, one must also consider the worst. Artificial organisms could escape into the wild and cause environmental havoc or be turned into biological weapons. The door is open. Knowledge is now accessible to all.

The genetic code is hackable. Our current version of *Homo sapiens* 1.0 is the story of little variations (mutations) that keep popping up during the course of the reproductive process. However, *Homo sapiens* 1.0 is unlikely to be the end point of humanity's Darwinian evolution. From now onward, human genetic variants or the lack thereof will not evolve solely because of natural chance (random). It will be self-designed. *Homo sapiens* 2.0 is just a matter of time. REIs should be prepared to understand and participate in the global task force of decision-making. This process must be driven by scientific and ethical principles.

The events of 2018 highlight the important role REIs must accept. The headlines announcing the birth of gene-edited twins in China brought all responsible individuals to pause and consider the potential consequences. The premature clinical application of germ line gene-editing had progressed at warp speed. The unethical experiments were apparently performed in "our" specialty with tremendous ease and may have remained undetected by the treating in vitro fertilization physicians. Although the true details may never be known, the primary scientist responsible was a Chinese biophysicist who has since been sentenced to prison (3). The ease with which the first known human germ line gene-editing was accomplished deserves consideration. It is as simple as an additional microdroplet containing CRISPR-Cas9 being added during the intracytoplasmic sperm injection by a willing embryologist. A series of recent publications have demonstrated that although technically straightforward, attempts at CRISPR-Cas9-mediated germ line gene-editing in human embryos can have serious unintended consequences (4). The off-target effects include segmental and whole chromosome deletions as well as hemizygous indels. The unbelievable pace of ongoing scientific innovation will nevertheless offer solutions to these newly discovered limitations.

Unfortunately, the current regulatory environment in the United States prohibits federal funding for basic research that is needed to understand DNA repair mechanisms in the human embryo. Since 1996, the recurring rider known as the

Dickey-Wicker Amendment prohibits the use of federal funds for research in which a human embryo is modified to include heritable genetic modification (5). This effectively precludes the conduct of appropriate translational research under the watchful eye of the National Institutes of Health and the peer-review process.

Why does human germ line gene-editing matter? The professional and public outcry should serve to promote a wider examination of how transformative genomic technologies are currently being applied across reproductive medicine and humankind. Current clinical practice allows physicians and patients to select a "healthier" embryo for transfer. In time, future genetic engineering will produce self-designed embryos for different reasons that will produce future human beings (*Homo sapiens* 2.0).

In contrast to the relevance of these enormous challenges, REIs remain conspicuously absent from the greater clinical, scientific, and bioethics debate regarding germ line gene-editing. The clinical implementation of novel technologies comes with our own inherent biases and/or reduced understanding. Many REIs finished their formal training before the completion of the human genome project, and most of them before the introduction of next-generation sequencing, the ultimate technology combining automated DNA sequencing and computational analysis. Yet, we are the only physicians with direct experience in working with human embryos on a regular basis. Our field is the entry point to these genetic advances in human history. Reproductive biology is no longer a matter of chance. Our specialty requires physicians who understand genomics and are willing to discuss the difficult ethical, social, and legal considerations thereof.

Trust has been greatly eroded in all aspects of our lives recently and science is no exception. At times, our specialty is viewed with mistrust by bioethicists, patients, the media, and many others. As humans, we must always be inquisitive and humble about our knowledge, we should be aware that we are an aggressive and hubristic species that has always pushed our limits. We now have all the genetic makeup of our species. Regardless of the fights between "the guardians of faith" that want to avoid any genetic intrusion in our life and the "progressist extremist" including the reckless who think that an end justifies the means, the realization is inevitable sooner rather than later.

The primary responsibility of REIs lies with our patients, who place their trust in our recommendations. This requires speaking up, especially because silence can be misinterpreted as acquiescence in the implementation of this genetics revolution in reproductive medicine. The REI community should participate in all ways possible in the guidance of the technological, clinical, and ethical values of this oncoming revolution.

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