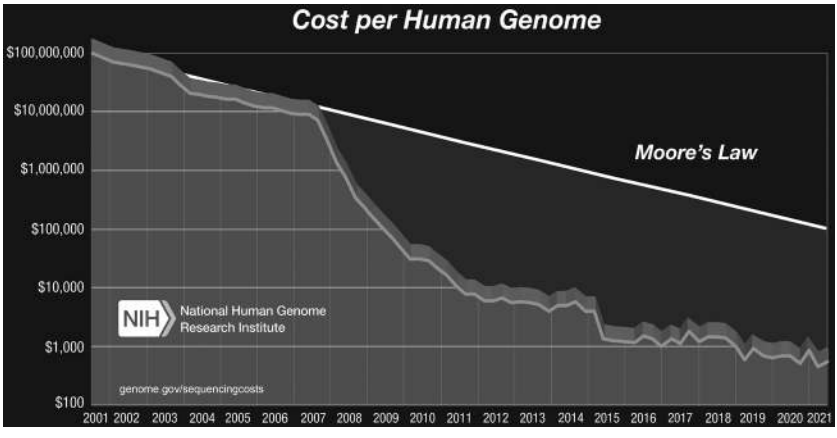
Prologue

Revolution, Transition, and Transformation

On May 31, 2007, at a ceremony in Houston, Texas, biotechnology scientist and entrepreneur Jonathan Rothberg handed a hard drive tied with a simple red ribbon to James Watson – a Nobel Laureate for co-discovering the double-helix structure of DNA, and the chief architect of the Human Genome Project/HGP.[1] When Watson accepted that hard drive in the palm of his hand, he became "the first of the rest of us" to receive the DNA sequence of his entire personal genome.[2]

Rothberg's company, 434 Life Sciences, sequenced Watson's genome in collaboration with Dr. Richard Gibbs, Director of the Human Genome Sequencing Center at the Baylor College of Medicine. They used the first "next-generation sequencing"/NGS technology – DNA speed-reading technology with the potential to impact genome analysis the way microprocessors enabled computing beginning in the 1960s.[3] A handful of scientists accomplished this feat in four months and at a cost of less than $1.5 million.[4] In comparison, the draft human genome sequence completed in 2003 through HGP – our genetic common denominator drawn from several individuals' genomes – was a global undertaking compiled through the concerted efforts of more than a thousand researchers across six nations, took approximately thirteen years to complete, and consumed $2.7 billion (FY1991 dollars) in US government funding alone.[5]

Genomic sequencing capacity has continued to soar and its cost to plummet by multiples in the years since Dr. Watson was handed his personal genome sequence. Rothberg predicted then that "sequencing throughput would grow at least fivefold over the coming years …."[6] His prediction was realized, as graphed by the National Human Genome Research Institute/NHGRI:[7]



Source: www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data

Moreover, "Innovation in genome-sequencing technologies and strategies does not appear to be slowing."[8] The National Academies of Science, Engineering, and Medicine/NASEM recognized the same in 2017 after comprehensively surveying the biotechnology landscape spanning into a ten-year horizon.[9]

At the time the Houston ceremony took place (2007), leaders in the field gauged the threshold price for critical mass consumer consumption of whole genome sequencing at $1,000. "[T]he figure emerged as a mythic technological totem in the world of genetics, sending a generation of DNA geeks chasing after it for the better part of the 21st century."[10] Illumina, Inc. and Veritas Genetics reached that $1,000 price point in 2014, Veritas began selling consumers their full personal genome sequences for $999 in 2016, and other companies followed.[11] By 2018, more than a million people had purchased their whole genome sequences.[12] Subsequently, the science community's quest shifted from realizing the $1,000 personal genome to realizing the $100.00 or less personal genome, sequenced within minutes with extreme precision through dozens of proofing runs, and by standalone computer hardware that fits comfortably on the corner of a desk – "in the not-too-distant future."[13]

The ability to generate medical meaning from sequenced DNA – the overarching, long-term mission of HGP, Watson, Rothberg, their science contemporaries and progeny, and now millions in the biopharmaceutical ("biopharma"), medical, and patient communities – is amassing along with the advancement of sequencing technologies.[14] With completion of a draft sequence of the human genome came the epiphany that, not only are we are 99.9 percent the same genetically (all of our genetic variation is attributable to one-tenth of one percent of human DNA), but our genetic variation is attributable to a currently estimated 20,500 active (protein-coding) genes.[15] Yet, the scope of tangible, observable human variation – from physical differences to the occurrence of diseases, to responsiveness to prescription biopharmaceuticals, and well beyond – remains very real. Genes multi-task

exponentially more than anticipated prior to HGP, and perspective about gene function has shifted. Scientists have a significantly heightened appreciation for the dynamism of genetics, the intricacies of genetic expression, and ongoing, pervasive interactions among genes, proteins, and environmental influences, as well as gene interactions with each other.[16] Genes multitask – often dizzyingly so. Throughout our lives, each of us is a simmering, swirling pot of genomic gumbo, with constantly changing conditions and ingredients (environmental influences) added continuously.

Given this level of genetic intricacy, complexity, and dynamism, DNA samples and accompanying medical information – typically, voluminous amounts of both – are the means to make medical and clinical sense out of the human genome. As explained by Eric Lander, a trailblazer in the DNA sequencing world who joined forces with Dr. Francis Collins in the US government effort to map the human genome, "You have to compare genomes to learn anything … maybe between dozens or hundreds or of people with a disease or without a disease."[17] In fact, gathering accurate, reliable personal health and lifestyle data is the primary challenge for human health application. As Anne Wojcicki, co-founder and CEO of 23andMe, the seminal direct-to-consumer/DTC personal genome health services/PGHS company, relayed to researchers during an event on the company's campus in May 2019, "Anyone can go get genomes. What's really hard is phenotypic [observable characteristics resulting from interaction between one's genotype and environment] data."[18] Managing voluminous phenotypic data poses another daunting challenge. According to Sean Harper, Amgen's executive vice president for research and development/R&D, Amgen invested more than a billion dollars over nearly two decades to develop the capability to routinely extract data necessary to validate and invalidate drug targets, but "The hard part is to get all these medical records and lab tests curated in a computer system where they are query-able and to perfect the analytics."[19]

As you read this sentence, legions of scientists around the world are translating the human genome's three billion nucleotide base pairs (the "As, Cs, Gs, and Ts" for the compounds adenine, cytosine, guanine, and thymine) into the medical meaning necessary for precision medicine (treatments tailored to a person's genome) and personalized medicine (treatments derived from a person's genome). They are working at an ever-quickening pace.[20] For example, the ongoing Personal Genome Project/PGP, initiated in 2005, embodies a "coalition of projects across the world dedicated to creating public genome, health, and trait data."[21] The PGP global network of participants includes Harvard PGP, PGP Canada, PGP UK, Genom Austria, and PGP China.[22]

Governments, industry, and academia have been gathering the DNA samples and related health information needed for translation for some time, on a constantly widening scale and with increasing intensity. The business of biobanking – the organized, typically large-scale ("population genetics" and "population genomics") collection of DNA samples and associated medical information – has matured into a multifaceted, diverse, and global endeavor.[23]

The US government is an ambitious biobanker.[24] The Department of Veteran Affairs has been building the Million Veteran Program/MVP since 2011 and, as of 2019, had recruited 650,000 veterans and collected years of their medical records, including physician prescription data.[25] The US also launched the Precision Medicine Initiative/PMI in 2015, renamed the All of Us Research Program ("AllUs") in 2016, with $130 million allocated to NIH to build a national cohort of research participants, and $70 million allocated to the National Cancer Institute for genomics (the study of gene function in the context of a genome, which is an organism's complete set of genes) in oncology through the Center for Cancer Genomics/CCG. AllUs is a NIH undertaking to recruit a cohort of a million or more residents in the US representative of the nation's population diversity.[26] AllUs participants agree to give blood samples, to have their genomes sequenced, to provide medical and lifestyle information and, potentially, to wear devices to continuously track their vital signs and monitor their physical activity. The goal of the program is that, "[b]y taking into account individual differences in lifestyle, environment, and biology, researchers will uncover paths toward delivering precision medicine."[27] Congress budgeted $230 million for AllUs in 2017 and, on a scale somewhat comparable with HGP ($3 billion spread over fifteen years) given the advancement of related technologies (notably, next-generation sequencing/NGS) and genomics since HGP was launched in 1990, authorized $1.455 billion over ten years. Reminiscent of HGP and the Manhattan Project during WWII, AllUs "has contracted with scientists at just about every leading university, as well as with companies like Verily, a subsidiary of Alphabet Inc. – the conglomerate parent of Google."[28]

Several US-based for-profit companies also are major biobankers, including Amgen Inc. – a 1980 California start-up that ranked 129 on the 2019 (prior to the COVID-19 pandemic declaration) Fortune 500 List.[29] In 2012, Amgen purchased deCODE Genetics, Inc., the holder of a biobank of DNA samples and substantial medical information inclusive of approximately 160,000 Icelanders – nearly half of the island nation's entire population – for $415 million.[30] Regeneron Pharmaceuticals, Inc., another leading US biotech company, established The Regeneron Genetics Center®/RGC, which is a genomics "big data" enabling technology provider engaged in multiple biobanking efforts, both public and private. For example, RGC is the catalyst for a consortium among AbbVie, Alnylam Pharmaceuticals, AstraZeneca, Biogen, and Pfizer to accelerate drug R&D by mining genomic sequence data and medical information from the UK Biobank's 500,000 participants.[31] Kaiser Permanente and Geisinger Health Systems/GHS, two large US health care providers with direct access to vast cohorts of patients and their medical information, also are engaged in large-scale biobanking.[32]

The fusion of genomic sequencing technologies and the phenotypic riches of biobank data generates genetic testing capabilities with predictive health implications, which is commonly referred to as "genetic wellness" and "genetic health risk/GHR" testing.[33] The commercial sector providing consumers with these personal genome

testing services is burgeoning economically and transforming culture, medicine, and health care.[34] Even with DNA sequencing costs plummeting as capacity soars (more testing potentially available to consumers at declining prices from the same DNA sample), the global genetic testing and consumer wellness genomic market, valued at $2.24 billion in 2015, has been projected to double by 2025.[35]

On April 6, 2017, the US Food and Drug Administration/FDA granted an application submitted by 23andMe to market a portfolio of direct-to-consumer, genetic-health risk/DTCGHR testing services, which included genetic markers for Alzheimer's Disease and Parkinson's Disease.[36] 23andMe's DTCGHR testing is offered to consumers through its Personal Genome Health Service/PGHS, which makes physician and other learned medical professional involvement wholly consumer optional.[37] Under the 23andMe business model for DTCGHR testing, individuals purchase kits, send their DNA to the company through the mail, and access their personal GHR information through an internet portal without any requisite physician or other learned medical professional involvement. Subsequently, millions of consumers have embraced the opportunity to take genome science and its medical interpretation into their own hands – to delve into their personal genomes for health decision-making – and demand is on the rise.[38] Consumers, investors, the FDA, and biopharma collaborators have proven responsive to 23andMe. As of July 2018 (less than fifteen months after the FDA approved the company's first physician-free DTCGHR tests), some five million people had purchased kits from and submitted their saliva to 23andMe for GHR testing.[39] 23andMe became a flagship company in a robustly emerging DTC personal genome testing global sector:

> Equity firms are pouring fortunes into these companies, not just because of the testing kits they sell but the personal information they collect, which can be shared and monetized. It's all happening amid a patchwork of laws and regulations that predate the growth of direct-to-consumer DNA testing.[40]

On June 17, 2021, through a merger, 23andMe was renamed 23andMe Holding Co. and became publicly traded on NASDAQ.[41] On November 1, 2021, 23andMe Holding acquired Lemonaid Health, a national telemedicine and digital pharmacy company, to overcome physician skepticism and uncertainty about its PGHS reports and, on August 9, 2022, the company declared "expan[sion] beyond its core consumer genetic testing into a new business line called its genomic health service."[42]

The FDA's market approval of DTCGHR testing without requisite medical professional involvement, beyond a milestone for 23andMe and its investors, was a rite of passage in an ongoing transition in the practice of US medicine – a transition to personal genome medicine/PGM that predates and will transcend the FDA's 2017 DTCGHR decision by decades.[43] Revolutions triggered by scientific advancements, such as the biotech revolution that began in the 1980s and the information and communication technology/ICT revolution that began in the 1990s (merger of the two

and the advancement of DNA sequencing technologies seeded a genomic revolution and advanced personal genome testing and genomic medicine), cause seismic change with momentum to continue over time.[44] US enactment of technology transfer law and policy/TTLP in 1980 incentivized collaboration and responsiveness to biotech R&D among government, academia, industry, and investors.[45] In fact, TTLP motivated a genomic revolution that rages on and into clinical medicine.[46] The creation of vaccines to protect against COVID-19 and the development of CRISPR technologies – a gene editing toolbox of technologies that already includes some that are surprisingly user-friendly – are the latest phase in this innovation revolution and mark the beginning of the next one.[47] The ICT revolution of the 1990s was triggered by the convergence of explosive scientific advances in digital computing and telecommunications.[48] ICT technologies/ICTs fundamentally changed how people, businesses, and governments communicate, interact, and work.[49] Human health transitions brought about by the application of scientific innovation, such as doubling the average human lifespan between 1920 and 2020, are the culmination of incremental changes over time.[50] The net effect of both revolutions and transitions brought about by scientific innovation is transformation with ethical, legal, and social implications. The architects of HGP recognized as much and complemented mapping the human genome with an Ethical, Legal, and Social Implications/ELSI Research Program counterpart to HGP.[51]

The US medical profession and the practice of medicine have undergone several defining transitions during their evolution since the late nineteenth century, which have proven transformative.[52] At the turn of the twentieth century, an apprenticeship-based profession formalized itself through requisite, standardized medical education with a clinical component, licensure, and credentialing, and became recognized and esteemed as a learned profession.[53] The medical profession assumed the role of sentinel over the science and evidence base of US medicine, earned deference and trust in that role, and became a self-regulating profession devoted to protecting and promoting the practice of medicine and individualized patient care.[54] The sanctity of the doctor–patient relationship became recognized and respected, with medical provider commitment to individualized patient care.

The infusion of medical science advancements during the twentieth century that improved human health substantially fortified the medical profession's influence and sovereignty; the profession became the trusted conduit for responsible clinical uptake of science innovation.[55] The doctor–patient relationship became a sanctified domain for individualized patient care dominated by learned and licensed medical professionals.[56] Beginning in the 1980s, the proliferation of managed care and the biotech revolution integrated government, academia, and industry in both science and medicine.[57] The reach of the World Wide Web and the consumer availability of personal computers enabled internet communication and networking during the 1990s, which fueled a global ICT revolution that permeated government, business, society, and culture.[58] By the end of the millennium, a social media movement was

amassing and drawing in generations from Millennials (born from 1981 to 1996) to Baby Boomers (born from 1946 to 1964).[59] Generation Z ("Zoomers" born from the mid-1990s into this millennium) gained awareness with ICT and social media – information and communication readily accessible through the strokes of computer keys and mobile phone keypads – as norms. Medical professional filters no longer restrained the flow of science and medical information. The culmination of these forces inspired a participatory health movement fueled by DTC biopharma marketing and internet access to science and medical information, which gained momentum in this millennium and now embraces DTC personal genome testing, personal genome autonomy, and patient self-determination.[60]

Extensive media coverage of the HGP and DNA in the years leading to the project's completion of a draft human genome sequence in 2003 and the subsequent infusion of tangible clinical applications of genomic medicine, such as elevated precision medicine and personalized medicine including life-saving oncology immunotherapies, have changed public perception of genetic testing.[61] Apprehension about commercial DTC genetic testing services for BRCA1 and BRCA2 (genetic variations, or alleles, associated with breast and other cancers) introduced in 1996 inspired forty-four states to enact legislation addressing genetic privacy, genetic discrimination, or some combination of the two by early 1999.[62] By 2010, US law and policy established federal medical privacy rights and barred genetic discrimination and health insurers from considering preexisting conditions, which quelled anxieties about genetic information prevalent in the 1990s.[63] Familiarity with DNA conceptually and experientially made DTC genetic testing much more comfortable. Recreational genetics for ancestry was socially and culturally popular early in this millennium, which incentivized US corporate and consumer citizens to undertake DTCGHR testing.[64] As observed by James Watson, "DNA has moved from being an esoteric molecule of interest to only a handful of specialists to being the heart of a technology that is transforming many aspects of the way we all live."[65] "It's in my DNA" is an often-used colloquialism, DNA ancestry kits have been one of the "it" gifts for years (Christmas, Mother's Day, Father's Day, and just because), and now there is the option of adding GHR information.[66] Media coverage of science responsiveness to the COVID-19 pandemic has further familiarized and normalized DNA and genomics in US perception and culture.

23andMe's Anne Wojcicki envisions that personal genome technology will transform health care. In her words, "The mission of 23andMe is not just about genetics. We have research, and again, all of that which is already a big mission, but we really want to transform health care."[67] 23andMe's mission is to empower individuals to exert unprecedented control over their health care through DTCGHR testing, and to realize consumer-centric personal genome medicine/PGM. Wojcicki, Watson, and numerous other influencers in genomics anticipate a health care system in which individuals bring their personal genome data to physicians and other medical professionals at their discretion to enable them to make their own health care decisions.[68] Our

entire personal genome sequences already are available for purchase at a price point manageable for many millions of consumers.[69] It is inevitable that we each will have increasing access to our personal genomes and related health information – to insights pulled from the pages of our present and "future medical diaries."[70] James Watson predicts that "The future will surely be one of ubiquitous genomics and real-time information that will transform public health and individual medical treatment."[71]

Expansion of the genetic health testing portfolio available to individuals – whether the testing is clinically and medically decisive, interpretive, or speculative – is opportunity for each of us to learn more about our personal genomes, to increase our medical autonomy, and to take more control over our health and health care. PGM *will* transform US medicine and our health care system. The core question is not whether, but *how* we make this transition and realize the PGM transformation. The sentiment of Watson, shared by Wojcicki and many now working at the forefront of PGM, is that "It cannot come too soon."[72] In fact, it can if clinically sound, responsible science and evidence-based medicine is undermined during the transition to PGM to the detriment of patient health and the practice of medicine.

Law is a discipline that defers to, protects, and builds upon precedent, and deference to the past is readily apparent in US regulation of the practice of medicine. The US federal government, including the FDA, restrains from intruding on the practice of medicine and doctor-patient decision-making – as recognized under US law for over a century. In 1925, the Supreme Court held that, "[o]bviously, direct control of medical practice in the States is beyond the power of the Federal Government."[73] The medical profession's sovereignty is illustrated vividly in physician discretion to prescribe FDA-approved drugs off-label, meaning independent of the clinical data relied upon by the FDA to put them on the market, and the extent to which US physicians exercise that discretion.[74] Consider physician opioid prescribing practices well beyond the scope of the FDA's approved use and the conditions the agency imposed through labeling, product inserts, guidance documents, and warnings during the approximately fifteen-year escalation of the nation's opioid addiction problem into an undeniable public health emergency.[75] The US' learned physicians proved extraordinarily susceptible to fraudulent industry marketing.[76] They wrote prescriptions for opioids that enabled the epidemic as they directly witnessed it build well over a decade, patient-by-patient, within the sanctity of their doctor–patient relationships and individualized patient care.[77]

Twentieth-century reliance on the medical profession, physician–patient decision-making, and the FDA to protect patients and to ensure sound science and evidence-based medicine is misplaced in twenty-first-century US health care. While most of the medical profession's midcentury predecessors were independent solo practitioners whom patients often compensated out of their pockets, today's physicians are accountable to businesses and health care networks under pressure to be cost-effective and profitable.[78] Patients, "informed" through DTC biopharma marketing, their internet searches, and social media are often demanding consumers of physician services.[79] US

law remains deferential to the sanctity of the doctor–patient relationship and individualized patient care, but the learned professionals in those relationships, unlike their last-century predecessors, are subject to the demands of "self-learned" patient consumers.[80]

US medical profession adherence to science and evidence-based clinical practice as the epicenter of good medicine, which became the primary catalyst for the evolution of both the medical profession and the practice of medicine during the twentieth century, is even more essential in PGM.[81] The scope of PGM spans the human genome and is all-inclusive of human health, and genomics is an ongoing deluge of dynamic science innovation in real time with dimensions of complexity.[82] "[T]aken together, the relations of genes, organisms, and environments are reciprocal relations in which all three elements are both causes and effects."[83] Genomics with adherence to evidentiary science-based medicine has been the means to counter the ongoing global COVID-19 pandemic – the deadliest pandemic in over a century, and the cause of global social and economic disruption, including the largest global recession since the Great Depression.[84] The unabashed politicization of science by the Trump Administration during the COVID-19 pandemic made the vulnerability of the science and evidence base of medicine all too vivid.[85]

Today's medical profession has far less control over the evidentiary-science base of medicine and industry has much more.[86] The primary mechanisms relied upon by the medical profession to protect the base of medicine are ongoing, rigorous scrutiny and uptake of medical science innovation through peer-reviewed medical journals (the "medical journal establishment/MJE") and control of the content and quality of ongoing medical education by the profession's most preeminent.[87] Although the overwhelming complexity of contemporary medical science has increased dependency on the MJE and esteemed medical profession influencers, these mechanisms have lost much of their reliable objectivity.[88] The biopharma industry finances and controls clinical research, which is the content fodder for the MJE.[89] Today's MJE is financially dependent on biopharma advertising, sponsorship, and reprint purchases for distribution to those who provide clinical care to incentivize use, including off label uses.[90] At the outset of this millennium, the MJE self-acknowledged its unreliability on its own pages:

> In September 2001 an unprecedented alarm was sounded. The editors of 12 of the world's most influential medical journals, including the *Journal of the American Medical Association*, the *New England Journal of Medicine*, *The Lancet*, and the *Annals of Internal Medicine*, issued an extraordinary joint statement in their publications. In words that should have shaken the medical profession to its core, the statement told of "draconian" terms being imposed on medical researchers by corporate sponsors. And it warned that the "precious objectivity" of the clinical studies that were being published in their journals was being threatened by the transformation of clinical research into a commercial activity.
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> The editors said that the use of commercially sponsored clinical trials "primarily for marketing … makes a mockery of clinical investigation and is misuse of a

powerful tool." Medical scientists working on corporate-sponsored research, the editors warned, "may have little or no input into trial design, no access to the raw data, and limited participation in data interpretation."[91]

The integration of academia, industry, and government through TTLP introduced in 1980, which enabled the genomic revolution and development of novel mRNA COVID-19 vaccines in a year, is prevalent in both clinical research and clinical care. Interactions between industry and renowned influencers in science and medicine are commonplace, and the biopharma sector is a generous sponsor of research studies, consulting agreements, speaking engagement honoraria, and continuing medical education/CME.[92] The biopharma sector also invests heavily in direct-to-physician/DTP marketing – a practice welcomed under US law and policy, which recognizes biopharma DTP and DTC marketing as corporate free speech and continues to entrust the medical profession to protect and promote the evidentiary-science base of medicine with adherence to objective truth as it did throughout the twentieth century.[93]

The FDA, a government entity with all the associated political and budgeting vulnerabilities, must endure the full R&D impact of the genomic revolution by its regulatory charge and very existence. The agency, which is the *recipient* of corporate citizen-sponsored applications and associated data, has become financially dependent on the biopharma industry to accomplish its mission since the introduction of user fees under the Prescription Drug User Fee Act/PDUFA of 1992.[94] The agency has actively collaborated with industry since enactment of the Food and Drug Administration Modernization Act/FDAMA and PDUFA renewal/PDUFA II in 1997, as it was mandated to do.[95] FDAMA and PDUFA II imposed heightened regulatory transparency and accountability on the FDA and changed the agency's culture by expanding its mission to include efficiency, along with product safety and efficacy, to be accomplished through heightened responsiveness to industry, patient, and provider ("stakeholder") concerns about its timeliness.[96] Prohibited from interfering with the practice of medicine, the FDA is under a constant barrage of criticism from multiple industry sectors, patient advocates, the medical profession, influencers in academia (the disciplines of medicine, public health, science, business, and beyond), the media, and the public for allegedly impeding the availability of innovative new products with life, death, and overall human health consequences.[97]

Traditional US reliance on its medical profession to ensure science and evidence-based, responsible medicine without more federal government involvement is antiquated and misplaced in consumer-centric PGM.[98] The advent of FDA-approved DTCGHR testing with any learned medical professional involvement wholly consumer optional is a tangible indicator of the need to question the reliability of US regulation of medicine during this phase of the genomic revolution and into the foreseeable future. Overall, GHR tests are distinguishable clinically from other categories of medical device diagnostics due to the information they relay about susceptibility to non-onset medical conditions and the complexity and dynamism of genetic