Technological readiness and implementation of genomic-driven precision medicine for complex diseases

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Franks PW, Melén E, Friedman M, Sundström J, Kockum I, Klareskog L, et al. Technological readiness and implementation of genomic-driven precision medicine for complex diseases. J Intern Med 2021; 290: 602–620.

Abstract. The fields of human genetics and genomics have generated considerable knowledge about the mechanistic basis of many diseases. Genomic approaches to diagnosis, prognostication, prevention and treatment – genomic-driven precision medicine (GDPM) – may help optimize medical practice. Here, we provide a comprehensive review of GDPM of complex diseases across major medical specialties. We focus on technological readiness: how rapidly a test can be implemented into health care. Although these areas of medicine are diverse, key similarities exist across almost all areas. Many medical areas have, within their standards of care, at least one GDPM test for a genetic variant of strong effect that aids the identification/diagnosis of a more homogeneous subset within a larger disease group or identifies a subset with different therapeutic requirements. However, for almost all complex diseases, the majority of patients do not carry established single-gene mutations with large effects. Thus, research is underway that seeks to determine the polygenic basis of many complex diseases. Nevertheless, most complex diseases are caused by the interplay of genetic, behavioural and environmental risk factors, which will likely necessitate models for prediction and diagnosis that incorporate genetic and non-genetic data.

Keywords: complex disease, genomics, precision diagnostics, precision medicine, precision prevention, precision treatment.

*Equivalent contributions.
†Deceased.

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Introduction

The resolution, throughput and cost of genome sequencing are such that we can routinely apply these technologies at scale. This presents unprecedented opportunities for medical practice and studies of disease aetiology.

The application of genomics to the field of medicine to improve diagnosis, prevention, treatment and prognosis – genomic-driven precision medicine (GDPM) – has been widely discussed [1–6] and is becoming standard of care, particularly for cancer, rare diseases and adverse drug reactions. Table 1 defines key terms in GDPM and related resources.

The foundations of GDPM date back more than half a century to programmes screening newborns for phenylketonuria, which have since been extended to include many rare single-gene disorders. In the past two decades, genetic testing has become increasingly widespread in patients with a familial predisposition to certain diseases. For example, mutations in BRCA1 or BRCA2 indicate a high risk for breast and ovarian cancer and a mutation in HTT causes Huntington’s disease. Focus is now being placed on expanding GDPM beyond cancers and rare diseases to common diseases of complex aetiology [7].

Here, we discuss GDPM for complex diseases with emphasis on evaluating the clinical and technical readiness of a potential test that might benefit individuals with a complex disease. While genomics is likely to play a key role in future medicine, it is expected to do so in concert with demographic and standard clinical data (e.g. age, sex, past medical history, current health status, family history, non-genetic biomarkers and environmental exposures). As an example, the ‘Stockholm 3’ model successfully identifies males with high prostate-specific antigen levels as unlikely to develop an aggressive form of prostate cancer [8]. The model combines a polygenic risk score (PRS), plasma protein biomarkers and clinical data. Nevertheless, it is likely that genetic data are not useful or necessary for all types of precision medicine. Particularly, disease monitoring will probably instead rely on repeated assessments of other omics technologies.

This review summarizes the views of clinicians and scientists who specialize in GDPM of complex diseases within the framework of Genomic Medicine Sweden (GMS). The review focuses on the quality and clinical utility of available empirical data [9], with a particular focus on the degree of technological readiness [10]. We also consider how benefits, risks and acceptance by patients and clinicians can be appropriately evaluated, with a view to facilitate the translation of GDPM for complex diseases into clinical practice. Because GDPM may be useful across many medical specialties, we explored the basis of a generalizable framework for evaluating, testing and implementing GDPM for complex diseases in health care.

| Table 1  | Key concepts and learning resources |
|----------|------------------------------------|
| Term     | Background                         |
| GDPM (genome-driven precision medicine) | References [1–6] |
| Genetic conditions | https://ghr.nlm.nih.gov/condition |
| GWAS (genomic-wide association study) | References [74,75] |
| Human genetics | NLM Genetics Reference (https://ghr.nlm.nih.gov) |
| Preparing healthcare providers for genomic medicine | http://www.pathologylearning.org/resources |
| PRS (polygenic risk score) | References [7,17,76] |
| Rare genetic conditions | https://www.rarechromo.org |
| WES/WGS (whole exome/genome sequencing) | References [77–81] |

Complex diseases and genetic architecture

Common complex diseases include amongst others allergies, cardiovascular disease, type 1 and 2 diabetes mellitus, inflammatory bowel disease (IBD), Parkinson’s disease, stroke, schizophrenia, rheumatoid arthritis, multiple sclerosis and non-syndromic cancers. Although the global prevalence of these diseases varies, they typically have 1–20% lifetime prevalence (by contrast, single-gene/monogenic diseases generally occur in the prevalence range 0.0001–0.05%). Most complex diseases are considered ‘non-communicable’ and account for approximately 70% of all deaths...
worldwide and cause significant morbidity, thus account for the majority of healthcare costs [11].

For nearly all complex diseases, genetic risk is probabilistic and not deterministic (the latter being true for diseases caused by highly penetrant mutations). The risk of disease in monozygotic siblings of patients with many complex diseases is <50%, whereas in monogenic diseases such as Huntington’s, a monozygotic co-twin of an index case will almost always be affected [12]. This introduces complexity, as the degree of risk is more difficult to assess than the clear-cut presence or absence of a known pathological variant. The potential advantage is that increased genetic risk of a complex disease may provide opportunities for prevention or early detection and management, as variants in nuclear DNA remain stable across the lifecourse.

The term genetic architecture refers to the number, type and frequency of genetic variants (in cases and non-cases), as well as the risk they confer [13,14]. In monogenic disease, the genetic architecture is often very simple. In complex diseases such as Alzheimer’s disease, the architecture is multifaceted with early-onset forms caused by rare mutations (APP, PSEN1 and PSEN2) and late-onset forms caused by a combination of high-risk common variants (APOE), multiple low-risk common variants and other non-genetic exposures (e.g. age, sex, behaviour and environmental factors) [15].

Most germline DNA genetic tests used in clinical medicine are deterministic and are almost exclusively used to diagnose relatively rare conditions. By contrast, the use of genetic tests for more common complex diseases has shown great potential in some research settings but is yet to translate from research to clinical practice. A common way to characterize genetic risk for complex diseases is through PRSs [16]. A PRS is the sum of multiple (sometimes thousands of) genetic variants that individually confer small effects. Recent studies show that high PRSs convey large and potentially clinically relevant risks in adulthood for diseases such as cardiovascular disease and type 2 diabetes mellitus [17] or early disease onset, increased damage accrual and decreased survival in systemic lupus erythematosus [18].

**GDPM in clinical context**

Contemporary medicine is founded on empirical evidence, often from clinical trials that are considered generalizable to much larger patient populations. This assumes that the population average is sufficient to guide decision making for the individual patient. By contrast, GDPM often focuses on population subgroups with similar clinical or biological characteristics, thereby improving the ‘precision’ of the evidence. Although reducing error (i.e. increasing precision) in clinical decision making is a key objective of GDPM, it is also important to evaluate whether the specific GDPM recommendation is as (or more) cost-effective, safe, tolerable, accessible and acceptable as its contemporary medicine counterpart.

**Diagnostics**

As most complex diseases are heterogeneous in aetiology, genetics may aid diagnostics by identifying subgroups/subtypes within a conventional complex disease diagnosis that are distinguished by different aetiologies or risk trajectories, thus benefiting from targeted treatment. An example is ischaemic stroke with different aetiological subtypes (large vessel occlusion, small vessel occlusion, cardioembolic stroke or arterial dissections) each of which may have different genetic architectures requiring different targeted therapy and clinical follow-up. GDPM might also help identify rare conditions that are hidden within a complex disease diagnosis. For instance, approximately 3% of patients with chronic obstructive pulmonary disease (COPD) have alpha1-antitrypsin (AAT) deficiency [19]. AAT deficiency is most commonly caused by homozygosity for the SERPINA1Z allele and is strongly associated with COPD as well as hepatic cirrhosis and hepatocellular carcinoma [20]. If detected early, specific clinical surveillance and treatments are recommended.

**Prevention**

 Ideally, diseases should be prevented rather than treated. The phenylketonuria example mentioned above is one of the first examples of severe disease (albeit a monogenic disorder not a complex one). Although the disease itself is not preventable, the severe consequence of phenylketonuria (e.g. cognitive developmental impairments) can, through early detection and consequent adherence to a phenylalanine-free diet, be prevented. Other well-known examples are familiar hypercholesterolemia, which can be identified and treated to prevent coronary events [21], and BRCA1-2 genetic tests in breast cancer [22]. The clinical (or public health) use of GDPM in preventing common,
complex diseases is, however, yet to be explored for most medical areas (Table 2).

**Treatment**

GDPM may aid in selecting an optimal treatment for a specific patient. Patients can show substantial differences in treatment response for many common diseases. This is a major challenge in clinical medicine, and there is a wide gap between the need to match treatments to specific patients and available tools to predict clinical response or risk for adverse drug reactions. One of the first examples of GDPM is tyrosine kinase inhibitors that are beneficial in chronic myeloid leukaemia patients with a typical chromosomal translocation [23]. GDPM can also be used to predict effect (positive or adverse) of common drugs. A certain drug or dose may be harmful due to individual variation in for example pharmacokinetics, which was the traditional focus of pharmacogenetics. The Clinical Pharmacogenetics Implementation Consortium (CPIC) was initiated to facilitate the use of pharmacogenetics by reviewing all evidence and producing guidelines to improve choice of drugs or dosing within diverse areas, and cover for example psychoactive, antithrombotic, gastrointestinal, anti-inflammatory and cholesterol-reducing drugs [24]. CPIC also has guidelines for immune-mediated risk of serious adverse reactions to certain drugs. For instance, individuals carrying a HLA-B variant (HLA-B*15:02, common in those of East Asian ancestry) should avoid the anticonvulsant carbamazepine due to high risk of Stevens–Johnson syndrome or toxic epidermal necrolysis [25,26]. Additionally, multiple ‘biologics’ (biopharmaceuticals) have emerged as effective therapies for a range of inflammatory diseases (e.g. rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis and asthma). Some are extremely expensive and others have rare but devastating adverse drug reactions. Hence, there is an urgent need for predictive biomarkers to guide appropriate treatment selection and to minimize harm.

**Prognosis**

Genes that influence disease prognosis may be different from those affecting disease risk. From a clinical point of view, assessing the likelihood of an exacerbation, flare-up or general deterioration is of utmost importance in order to tailor treatment and follow-up regimens. Recent evidence suggests that genetics may aid in identifying patients at risk of a more severe disease (e.g. SLE [18]) or prognosis in ageing patients (e.g. with a minor stroke [27]). Using transcriptomics data, a newly developed PCR test for IBD prognosis (PredictSURE IBD™) is now prospectively examined in a large intervention trial [28] (Table 2).

**Field review**

*Table 2* shows a summary of narrative reviews described in more detail in Supplemental Text S1. These reviews focus on technological readiness (i.e. how rapidly a test can be implemented into health care) of GDPM across many of the most burdensome contemporary complex, chronic diseases (cancer not included with the exception of breast cancer, as an example). The levels of technological readiness are as follows: none/poor=absence of data or proof (e.g. a plausible but untested idea) or investigational (a few supportive studies exist or are ongoing, but the data are insufficient to warrant confident conclusions), good=sufficient evidence to support an adequately powered clinical evaluation (the data strongly support the clinical utility of a test), moderate=clinical use has started but is not fully implemented and excellent=a GDPM test is in clinical use in multiple countries.

The review shows that fields like cardiology (particularly diagnosis of cardiomyopathies and diagnosis and prevention of aortic disease), endocrinology (particularly subclassification of type 2 diabetes), obstetrics and gynaecology (prediction of foetal and maternal morbidity) and psychiatry (diagnosis of autism and intellectual disability) have a high degree of technological readiness regarding diagnostics, prevention, therapeutics or prognostics. As examples, the following section describes ongoing GDPM work in two specific disease areas in more detail: cardiology and endocrinology.

**Cardiology examples**

Coronary artery disease (CAD, also known as ‘coronary heart disease’) is a leading and increasing cause of death worldwide. CAD is a complex disease influenced by multiple genetic, behavioural and environmental factors. Large genome-wide association studies (GWAS) have identified over 150 loci associated with CAD [29,30]. Although these loci each convey small effects, the
| Medical area         | Classification | Example                                                                 |
|---------------------|----------------|-------------------------------------------------------------------------|
| **Allergy / Respiratory** | Moderate       | A PRS comprised of several variants can identify a small subset of individuals at markedly increased risk for moderate-to-severe COPD [82]. In addition, AAT deficiency, most commonly caused by homozygosity for the SERPINA1 Z allele, is strongly associated with COPD (as well as hepatic disease). If detected early, specific clinical surveillance and treatments are recommended [20]. |
| **Cardiology**      | Excellent       | Panels for cardiomyopathies, including arrhythmogenic ones, routinely used in Sweden [43]. |
|                     | Good            | Familiar hypercholesterolemia can be identified and treated to prevent coronary events [21]. |
|                     | None            | None                                                                     |
| **Endocrinology**   | Good            | Classification of type 2 diabetes using clinical traits identified 5 subclasses with divergent prognoses has been performed in Swedish and | Moderate | The clinical utility of FRS is currently being evaluated in osteoporosis, but it may improve screening by identifying a subset None None |
Table 2. (Continued)

| Medical area | Classification | Disease prevention | Disease treatment | Disease prognosis |
|--------------|----------------|--------------------|-------------------|-------------------|
|              | Example                     | Example                        | Example                                  | Example                                  |
| Diagnostic   | Finnish cohorts [49], with widespread replication. | of high-risk individuals who might particularly benefit from osteoporosis therapy | [56,57]. |          |
|              | Similar studies have been performed using genetic classification [50] [86]. | | | |
| Gastroenterology | Good | Lipid signature associated with NAFLD and the amount of liver fat, first reported in Belgian and Finnish cohorts [87], with multiple subsequent studies reporting similar signature. | Poor | Moderate | Recent data from the Personalising Anti-TNF Therapy in Crohn’s disease (PANTS) cohort demonstrate that HLA-DQA1*05 is associated with development of antibodies to both infliximab and adalimumab [88]. Data have been confirmed in a retrospective cohort. | Moderate | Moderate | CD8 T-cell signature predictive of future disease course of IBD, defined as a need of escalation of therapy. The initial work was based on transcriptome data [89] and was followed by development and validation of a PCR-based test [90]. The test is now available as a CE-marked product PredictSURE IBD™. The test currently examined in the PROFILE intervention trial [28]. |
| Neurology    | Good | Early-onset Alzheimer’s disease (AD) driven by rare genetic variants with Mendelian inheritance patterns within families, accounting for <5% of AD patients, can be clinically tested for and diagnosed [91]. | Poor | A recent study found that a meta GRS for ischaemic stroke could identify a subset of individuals at monogenic levels of risk, but this finding needs replication [96]. | Poor | Moderate | Genetic counselling and screening for APOE ε4 are available, where homozygotes have a 15-fold increased risk to develop AD, but is generally discouraged as ε4 carriers do not necessarily develop AD [97,98]. |
|              | Pharmacogenetic studies investigating genetic variants in genes coding for dopaminergic receptors show individual fluctuations in response to administration of L-
### Table 2 (Continued)

| Medical area                  | Diagnostic Classification | Example                                                                 | Disease prevention Example | Disease treatment Example | Disease prognosis Example |
|-------------------------------|---------------------------|------------------------------------------------------------------------|----------------------------|--------------------------|--------------------------|
| **DOPA** and may hold promise for personalized treatments of Parkinson’s disease [92]. | Poor                      | Some genetic variants or other molecular signatures associate specifically to ischaemic or haemorrhagic stroke, and some to specific aetiological subtypes of ischaemic stroke. However, these cannot yet be used to aid diagnostics [93–95]. | Poor Genetic variants [99–101] and protein biomarkers [95] that predict stroke outcomes have been identified, but many need to be replicated and so far they add little prediction above clinical variables. | Poor | None |
| Obstetrics–Gynaecology       | Excellent                  | Since the first non-invasive prenatal testing (NIPT) was introduced as a maternal screening tool in clinical medicine for foetal trisomies 2011 [102,103], it has been used by millions of pregnant women. Today, it is a standard screening tool in Western clinical medicine and are expanding from trisomies to deletions and duplications and even a diagnostic tool for rare foetal mutations. | Excellent Pre-implantational genetic diagnosis (PGD) is used together with in vitro fertilization [104]. Genetic testing is performed before embryo transfer so that couples with a severe genetic disease in the family can select to transfer an embryo without the affected genes. This is clinical practice in high income countries today. | None | None |
| Pharmacology–polypharmacy in elderly | Poor                      | Moderate Older patients are at high risk of adverse drug events because of multimorbidity, polypharmacy and age-related changes [105]. | Moderate Pharmacogenetic profiling may improve safety of treatment, symptom remission and be cost-saving. Examples: Genotype- | Moderate | Moderate Pharmacogenetic profiling is a feasible way to improve prognosis in ageing patients. Examples: Genotyping predicts tamoxifen discontinuation |
### Table 2 (Continued)

| Medical area | Classification | Example | Disease prevention Example | Disease treatment Example | Disease prognosis Example |
|--------------|----------------|---------|----------------------------|--------------------------|--------------------------|
| **Diagnostic** |                |         |                            |                          |                          |
| Psychiatry   | Excellent       | WES of parents and affected child with moderate or severe autism and intellectual disability is standard of care in many centres, yield 25–60% [114] | Poor                      | None                      | None                      |
| Oncology     | Good            | 1–3% of adults with severe psychotic disorders will have a pathogenic copy number variants [115] | Good                      | Good                      | Poor                      |
| Breast cancer| Good            | The first paper on molecular subtyping of breast cancer was published in 2001 [116] | Good                      | The first genetic breast cancer susceptibility genes were identified in the early 90s (e.g. *BRCA1*, *2*) and an additional 10–15 rare, high penetrant mutations have been linked to an elevated risk of breast cancer | Poor                      |

- Personalizing medication by pharmacogenetics may prevent problems in ageing polypharmacy patients. Example: Re-hospitalizations and emergency department visits were reduced in patients who received pharmacogenetic profiling compared with those who received only traditional medication reviews [106].
- Guided warfarin initiation improves safety of treatment [107]. Genotype-guided antidepressant therapy is more likely to achieve symptom remission and is cost-saving [108,109].
- Genotype-guided fluoropyrimidine treatment improves safety of treatment and is probably cost-saving [110,111].
- Genotype-guided antiplatelet therapy improves prognosis after percutaneous coronary intervention [113].
- Genotype-guided antiplatelet therapy improves prognosis in patients with minor stroke/TIA and impaired renal function [27].

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Table 2 (Continued)

| Medical area | Diagnostic classification | Example | Disease prevention example | Disease treatment example | Disease prognosis example |
|--------------|---------------------------|---------|---------------------------|--------------------------|--------------------------|
| Rheumatology | Good                      | Genetic factors contribute to classification of distinct disease phenotypes in Rheumatoid arthritis (RA) [119–121] | None | Moderate | RA risk variants indicate pathways that are used by existing anti-RA drugs and are used to indicate new targetable pathways. |
|              | None                      | None    | (NEJM 2021, in press).    |                          |                          |

COPD, Chronic obstructive pulmonary disease; GRS, genomic risk score; IBD, inflammatory bowel disease; NAFLD, non-alcoholic fatty liver disease; SLE, systemic lupus erythematosus.
development of PRSs has helped identify patient subgroups at relatively high risk of disease. For example, Khera et al. [17] reported that individuals with a very high CAD PRS had risks similar to monogenic mutations. The authors also showed that CAD PRSs convey a greater predictive value than any conventional CAD risk factor (smoking, diabetes, obesity, hypertension, high cholesterol levels and family history), and added independent information to models that included conventional risk factors [31]. The PRS for CAD has since been validated in independent cohorts [32]. From a clinical perspective, this suggests that PRSs may be a useful tool for risk prediction in GDPM. However, most PRS was derived in European ancestry populations, potentially limiting the extent to which they can be generalized to other ethnic groups [33], and it remains unclear whether PRSs are useful when seeking to determine treatment responses. Thus, further work is needed to refine the predictive ability of PRS, particularly in the context of different treatments, and to improve the generalizability to other populations if this type of GDPM is to become clinically useful.

Genetics research has helped pinpoint genes that are important in CAD pathophysiology and identify novel therapeutic targets. Some specific, high-impact genes were identified in studies of familiar hyperlipidaemia and subsequent risk of CAD. These include genes such as *LDLR*, *PCSK9*, *APOB*, *LDLRAP1* and *ABCG8* [34–38]. For example, inactivating mutations in *PCSK9* cause a reduction in LDL cholesterol and decreased risk of CAD [39], and monoclonal antibodies to PCSK9 lower LDL levels dramatically and reduce risk for major cardiovascular events [40]. Therapies that target PCSK9 are now introduced in clinical practice guidelines.

Heart failure (HF) is a leading cause of hospitalization and death worldwide. HF results from many pathophysiological processes that adversely influence myocardial structure and function including CAD, hypertension and toxic agents such as alcohol. However, HF can also occur in the absence of any such process (idiopathic cardiomyopathy). A heritable contribution to HF is well established [41,42], and genetic testing is routinely performed for several familial forms of cardiomyopathy, mainly to reduce the need for targeted surveillance in families with hypertrophic and arrhythmogenic forms [43]. The recent recognition that protein-truncating variants in the titin gene (*TTN*) greatly increase risk of dilated cardiomyopathy may lead to wider implementation of genetic testing in HF, but further studies are needed to evaluate the clinical value of genetic information more precisely [44]. Results from GWAS for HF show a polygenic architecture [45], but testing for such variants has no clinical role today even though it may provide information on genetic modification for familial forms of HF, or add prognostic information that can guide treatment and clinical monitoring. A particularly important application for GDPM in HF may be a pharmacogenetic assessment to guide the increasingly complex therapeutic armamentarium for this condition (studies evaluating these approaches are currently in early stages).

The field of cardiology includes multiple other diseases with genetic architectures dominated by rare protein-changing variants of strong, clinically impactful, effects. For these conditions, genome sequencing is widely used in cardiology for diagnosis and treatment guidance for many cardiac diseases with autosomal-dominant heritability patterns, such as aortic disease, familial hypercholesterolemia and arrhythmia syndromes.

Endocrinology examples

Diabetes mellitus (DM) can manifest for a variety of reasons, and our understanding of its causal molecular and contextual factors is incomplete. The simplicity with which DM is diagnosed belies its highly complex nature and impedes its prevention and treatment. Type 1 DM accounts for ~10% of cases, type 2 DM accounts for ~90% [46], and ~1% of DM occurs in other contexts including gestational DM [47], rare monogenic forms of DM (e.g. mutations in the insulin gene), DM resulting from another disease processes (e.g. cystic fibrosis or pancreatitis) and drug-induced DM (e.g. glucocorticoid treatment) [46]. At present, GDPM is only applied to rare forms of DM (e.g. ‘maturity onset DM of the young’), where genome sequencing allows precise molecular diagnoses and targeted therapeutics.

Type 2 DM is diagnosed when all other known explanations for hyperglycaemia have been excluded. Its subsequent composite nature partly explains why prevention and treatment often fail – even the most impactful lifestyle and drug interventions (metformin) only delay DM onset by a few years on average [48]. Consequently, researchers have tried to refine the diagnosis of DM, for
example by reclassification based on combinations of clinical and/or genetic data. A machine-learning algorithm identified five DM subgroups defined by aetiological features (e.g. insulin resistance, insulin secretory deficiencies and other DM features) [49]. Other groups have defined probabilistic subgroups based on genetic data mapped to aetiological processes fundamental to DM [50,51]. Although clustering methods are highly informative from an aetiological perspective, none of the currently identified subgroups is able to compete with conventional analysis methods for predicting DM or its complications [52]. Nevertheless, more powerful data and analytical approaches could substantially improve subclassification of DM. Indeed, current major initiatives focus on characterizing human biological variation at multiple levels (e.g. transcripts, microRNAs, epigenetic marks, proteins, metabolites) and link these to the glycaemic deteriorations that precede DM and lead to complications [53].

Osteoporosis and related fractures are a major public health concern and result in a huge economic burden on healthcare systems. It is a complex disease influenced by multiple genetic, behavioural and environmental factors. Low bone marrow density (BMD) is the most important causal risk factor for fractures [54]. Fracture risk prediction subsequently combines clinical risk factors with analyses of bone mineral density (BMD) using dual-energy absorptiometry imaging. A large GWAS identified over 500 loci affecting BMD, explaining approximately 20% of its variance [55]. Genetic studies of many types of fractures identified 15 loci, all known BMD loci [54]. Future GWAS need to evaluate fractures categorized by bone site, and GWAS for other, non-BMD-related determinants of fracture risk (e.g. muscle strength, risk of falls) may identify additional genetic determinants useful for fracture prediction.

Several PRSs for BMD are available. A recent BMD PRS explained ~20% of variance [55,56], and a machine-learning algorithm developed a BMD PRS that explained ~23% of the observed variance [57]. These PRSs might identify a subset of high-risk individuals who might particularly benefit from osteoporosis treatment (for prevention or therapy), and their clinical utility is currently being evaluated. Although community-based fracture risk screening (clinical risk factors and a direct measure of BMD) can already reduce the rates of hip fractures in elderly women [58], the efficiency and accuracy of these screening programmes might be improved by adding a BMD PRS [57].

GDPM is already implemented for diagnosing rare but severe monogenic forms of paediatric osteoporosis due to osteogenesis imperfecta. Approximately 85% of these cases are caused by mutations in COL1A1 or COL1A2 [59]. Formerly, most clinicians screened for COL1A1 and COL1A2, but increasingly whole-genome sequencing (WGS) or targeted gene panels are used [59]. WGS of unique families with a clinically significant fracture history has identified novel forms of monogenic osteoporosis (e.g. autosomal-dominant osteoporosis caused by WNT1 mutations [60]).

Data analysis approaches for complex multidimensional data in GDPM

A major challenge for the implementation of GDPM is that for most patients, complex diseases result from the interplay of hundreds or thousands of gene variants, behavioural and environmental factors [13,161]. Indeed, patients with the same diagnosis may differ in risk factors and aetiology. In some respects, health care today is informed by fairly sparse data: diagnostics often rely on a limited number of laboratory and clinical variables determined at only a few measurement occasions. However, digital and genomic medicine promises to deliver far richer temporal data, mapping more of the complexity of common diseases and thereby allowing for diagnostics and therapeutics of potentially much higher efficacy. It is also possible that theoretical and computational advances will provide solutions to organize and analyse the data for clinical purposes [61].

As an example, network principles have great potential to describe and analyse a wide range of complex systems. For instance, protein–protein interaction networks or modules of co-expressed genes can be used as an organizing framework onto which disease-associated gene variants can be mapped [62]. These empirically defined networks and their structure can help us find central disease mechanisms, which can be exploited to find biomarkers and drug targets.

Another layer of complexity is that the effects of disease-associated genes vary across multiple cell types. Transcriptome-wide analyses of single cells are emerging as a method to address this problem. For example, single-cell RNA sequencing has been
proposed to have implications for personalized medicine in serious diseases with costly treatments [63]. Indeed, for these complex data, network principles have been shown to be applicable to prioritize biomarkers and drug targets [64]. Also, clinical variables, such as symptoms and environmental or social factors, may have important clinical implications. One study suggested that these variables can be integrated into complex biological models using network tools [65] [3,66–68].

There are countless other analytical approaches beyond network analyses relevant to GDPM, amongst which artificial intelligence (AI) is gaining considerable traction. As applied to GDPM, AI refers to a broad domain of computational methods that can be used to facilitate clinical decision making and improve the efficiency of screening protocols. AI is intended to mimic human patterns of inference, yet to do so more quickly, at lower cost and on a larger scale than can be achieved using conventional approaches. Machine learning (ML) is a subset of AI that seeks to answer specific questions often with iterative optimization algorithms, typically focused on reducing error and/or enhancing likelihood. AI includes a range of algorithmic domains in addition to ML (e.g. rules engines, expert systems and knowledge graphs). Deep learning (DL) is a subset of ML using deep artificial neural networks and deep reinforcement learning; DL algorithms are typically more computationally intensive than other ML algorithms and focus explicitly on improving computational accuracy. Regardless of the type of AI deployed, the quality of the results scales with the amount and quality of input data. To date, the most clinically relevant applications of AI have focused less on genetic data, and more on digital images and broad panels of biomarkers, the latter of which sometimes include genetic information. For example, AI has proven effective in undertaking rapid and high-throughput image evaluations to detect anomalies such as skin [69] and breast [70] malignancies, as well as optimizing scanning protocols to save time and reduce patients’ radiation exposure. More broadly, AI has been used in decision support systems for health care providers, for example by helping predict the onset of septic shock in intensive care patients [71]. AI is also showing promise for the prediction of early disease onset, for example by determining the probability of developing islet autoantibodies in type 1 DM [72], and for prognostication in those already diagnosed with disease, such as in the development of psychosis in patients with other high-risk psychiatric conditions [73].

Conclusions

Many medical areas have at least one GDPM test for a genetic variant of strong effect that is part of standard of care. This varies greatly across diseases, with GDPM in oncology, cardiology, endocrinology and prenatal/neonatal testing (obstetrics and paediatrics) notably advanced in this regard. The results of such tests provide clinical guidance in that they allow identification/diagnosis of a more homogeneous subset within a larger disease group. Alternatively, they can identify a subset of patients with different therapeutic needs and flag medicines that may offer substantial benefit or that should be avoided owing to high probability of adverse events. Some of these GDPM tests have strong supporting evidence but are not yet standard of care, often because the process of clinical implementation is yet to be defined (including infrastructure, education and point-of-care applications).

For almost all of these complex diseases, many patients do not carry known genetic variants of strong effect. However, intensive efforts to uncover their genetic basis have yielded promising and empirically supported GDPM test designs. Many are based on the clinical use of PRS. Because these diseases are caused by combinations of genetic and non-genetic exposures, GDPM models that combine clinical data, PRS, biomarkers (including large-scale omics data) and exposure information are likely to improve risk prediction or aid treatment decisions (e.g. the ‘Stockholm 3’ prostate cancer algorithm [8]). However, even when the efficacy of GDPM is proven, it will be necessary to evaluate cost-effectiveness, safety, tolerability, accessibility and acceptability relative to current medicines for the respective clinical question. Moreover, because the vast majority of human genetics research has been undertaken in people of European ancestry, studies of other ethnic groups are should be prioritized in the future, particularly where the discovery of rare variants is of interest. These evaluations will help ensure that GDPM aid to decrease health disparities, rather than increase them, which might happen if GDPM is inaccessible or poorly designed for those most in need. Ensuring all relevant stakeholders (e.g. patient representatives, caregivers, regulators, funders, pharma, etc.)
biotech, policymakers and health economists) are part of the process of developing and implementing GDPM will be critical to its success.

Acknowledgements

We thank Amrei Binzer-Panchal for editing the manuscript. We thank SciLifeLab for funding (Research Community Program 2018-2020). PFS acknowledges support from the Swedish Research Council (Vetenskapsradet, award D0886501), the US National Institute of Mental Health (MH077139 and MH1095320) and the European Union (COSYN, Horizon 2020 Program, RIA grant agreement no. 610307). IK acknowledges support from European Union (MultipleMS no. 733161 and EU-STAND4PM no. 825843). RR received funding from the Swedish Cancer Society, the Swedish Research Council, the Knut and Alice Wallenberg Foundation, Karolinska Institutet, Karolinska University Hospital and Radiumhemmets Forskningsfonder. PWF receives funding from European Research Council (CoG-2015_681742_NASCENT), Swedish Research Council, Swedish Heart-Lung Foundation, Swedish Foundation for Strategic Research (IRC Center) and the Novo Nordisk Foundation. EM is supported by grants from ALF, the H2020 Program ERA PerMed JTC 2018 Call (VR 2018-05619), the Swedish Research Council, the Swedish Heart-Lung Foundation and the Strategic Research Area Epidemiology at Karolinska Institutet. LR is supported by the Swedish Research Council, the Swedish Rheumatism Association, the King Gustaf the Vth 80-year Foundation and the Swedish Society of Medicine with the Ingegerd Johansson donation. MW is supported by grants from the Swedish Research Council (2018-03307), Swedish Heart-Lung Foundation (20170711) and Clinical Research Support (Avtal om Läkarutbildning och Forskning, ALF) at Uppsala University. CJ acknowledges support from the Swedish Research Council, Swedish Heart-Lung Foundation and the Swedish State under the agreement between the Swedish government and the county councils (the ALF-agreement). MFG receives funding from the Swedish Heart-Lung Foundation [20160872]; the Swedish Research Council [#2018-02837; #2014-03352; EXODIAB #2009-1039], the Swedish Foundation for Strategic Research (LUDC-IRC #15-0067) and IMI2 Joint Undertaking under grant agreement no. 115974 (BEAT-DKD), with support from the European Union’s Horizon 2020 Research and Innovation Programme and European Federation of Pharmaceutical Industries and Associations with JDRF.

Conflict of interests

PWF has received consulting honoraria from Eli Lilly, Sanofi Aventis, Novo Nordisk A/S and Zoe Ltd. He has stock options in Zoe Ltd, has received research support from multiple pharmaceutical companies as part of Innovative Medicine Initiative projects, and is an employee of the Novo Nordisk Foundation. PFS served as a scientific advisory board member of RBNC Therapeutics, served as an advisory committee member (grant recipient) of Lundbeck, served as a scientific advisory board member of Pfizer and received consultation fees from Element Genomics. RR received honoraria from AbbVie, AstraZeneca, Illumina, Janssen and Roche.

References

1 European Partnership for Personalised Medicine (EP PerMed), 2021, https://erapermed.isciii.es/wp-content/uploads/2021/02/Partnership_draft_document_EP_PerMed_2020_10_05.pdf
2 Cardon LR, Harris T. Precision medicine, genomics and drug discovery. Hum Mol Genet. 2016;25:R166-R172.
3 Njolstad PR, Andreassen OA, Brunak S, et al. Roadmap for a precision-medicine initiative in the Nordic region. Nat Genet. 2019;51:924-30.
4 Nice EC. The omics revolution: beyond genomics. A meeting report. Clin Proteomics. 2020;17:1.
5 Vargas AJ, Harris CC. Biomarker development in the precision medicine era: lung cancer as a case study. Nat Rev Cancer. 2016;16:525–37.
6 Collins FS, Varmus H. A new initiative on precision medicine. N Engl J Med. 2015;372:793–5.
7 Schork AJ, Schork MA, Schork NJ. Genetic risks and clinical rewards. Nat Genet. 2018;50:1210–1.
8 Gronberg H, Adolfsson J, Aly M, et al. Prostate cancer screening in men aged 50–69 years (STHLM3): a prospective population-based diagnostic study. Lancet Oncol. 2015;16:1667–76.
9 Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924–6.
10 Heder M. From NASA to EU: the evolution of the TRL scale in Public Sector Innovation. The Innovation Journa. 2017;2:1–23.
11 Global Burden of Disease Study. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390:1211–59.
12 Martin N, Boomsma D, Machin G. A twin-pronged attack on complex traits. Nat Genet. 1997;17:387–92.
13 Timpson NJ, Greenwood CM, Soranzo N, Lawson DJ, Richards JB. Genetic architecture: the shape of the genetic
contribution to human traits and disease. Nat Rev Genet. 2018;19:110–24.

14. Sullivan PF, Geschwind DH. Defining the genetic, genomic, cellular, and diagnostic architectures of psychiatric disorders. Cell. 2019;177:162–83.

15. Jansen IE, Savage JE, Watanabe K, et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer’s disease risk. Nat Genet. 2019;51:404–13.

16. International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature. 2009;460:748–52.

17. Khera AV, Chaffin M, Aragam KG, et al. Effects of a pharmacogenetic variant to patient stratification. Nat Rev Cardiol. 2018;15:748–59.

18. Sullivan PF, Geschwind DH. Defining the genetic, genomic, cellular, and diagnostic architectures of psychiatric disorders. Cell. 2019;177:162–83.

19. Marciñuk DD, Hernandez P, Balter M, et al. Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: a Canadian Thoracic Society clinical practice guideline. Can Respir J. 2012;19:109–16.

20. Silverman EK, Sandhaus RA. Clinical practice. Alpha-1 antitrypsin deficiency. N Engl J Med. 2009;360:2749–57.

21. Sturm AC, Knowles JW, Gidding SS, et al. Clinical genetic testing for familial hypercholesterolemia: JACC scientific expert panel. J Am Coll Cardiol. 2018;72:662–80.

22. Phillips EJ, Sukasem C, Whirl-Carrillo M, et al. Clinical pharmacogenetics implementation consortium guideline for HLA genotype and use of carbamazepine and ocarbazepine: 2017 update. Clin Pharmacol Ther. 2018;103:574–81.

23. Relling MV, Klein TE. CPIC: Clinical pharmacogenetics implementation consortium for the pharmacogenomics research network. Clin Pharmacol Ther. 2011;89:464–7.

24. Chen P, Lin JJ, Lu CS, et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N Engl J Med. 2011;364:1126–33.

25. Phillips EJ, Sukasem C, Whirl-Carrillo M, et al. Clinical pharmacogenetics implementation consortium guideline for HLA genotype and use of carbamazepine and ocarbazepine: 2017 update. Clin Pharmacol Ther. 2018;103:574–81.

26. Wu Y, Zhou Y, Pan Y, et al. Impact of CYP2C19 polymorphism in prognosis of minor stroke or TIA patients with declined eGFR on dual antiplatelet therapy: CHANCE sub-study. Pharmacogenomics J. 2018;18:713–20.

27. Parkes M, Noor NM, Dowling F, et al. PRedicting Outcomes For Crohn’s disease using a moLecular biomarkEr (PRO-FILE): protocol for a multicentre, randomised, biomarker-stratified trial. BMJ Open. 2018;8:e026767.

28. van der Harst P, Verweij N. Identification of 64 novel genetic loci provides an expanded view on the genetic architecture of coronary artery disease. Circ Res. 2018;122:433–43.

29. Nikpay M, Goel A, Won HH, et al. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. Nat Genet. 2015;47:1121–30.

30. Inouye M, Abraham G, Nelson CP, et al. Genomic risk prediction of coronary artery disease in 480,000 Adults: Implications for primary prevention. J Am Coll Cardiol. 2018;72:1883–93.

31. Wunnemann F, Sin Lo K, Langford-Avelar A, Busseuil D, Dube MP, Tardif JC, et al. Validation of genome-wide polygenic risk scores for coronary artery disease in French Canadians. Circ Genom Precis Med. 2019;12:e002481.

32. International HapMap Consortium. A haplotype map of the human genome. Nature. 2005;437:1299–302.

33. Abifadel M, Varret M, Rabes JP, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet. 2003;34:154–6.

34. Garcia CK, Wilund K, Arca M, et al. Autosomal recessive hypercholesterolemia caused by mutations in a putative LDL receptor adaptor protein. Science. 2001;292:1394–8.

35. Berge KE, Tian H, Graf GA, et al. Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. Science. 2000;290:1771–5.

36. Soria LF, Ludwig EH, Clarke HR, Vega GL, Grundy SM, McCarthy BJ. Association between a specific apolipoprotein B mutation and familial defective apolipoprotein B-100. Proc Natl Acad Sci U S A. 1989;86:587–91.

37. Lehrman MA, Schneider WJ, Sudhof TC, Brown MS, Goldstein JL, Russell DW. Mutation in LDL receptor: Alu-Alu recombination deletes exons encoding transmembrane and cytoplasmic domains. Science. 1985;227:140–6.

38. Cohen JC, Boerwinkle E, Moesly TH Jr, Hobbis HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med. 2006;354:1264–72.

39. Robinson-JG, Farrier N, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372:1499–99.

40. Lee DS, Pencina MJ, Benjamin EJ, et al. Association of parental heart failure with risk of heart failure in offspring. N Engl J Med. 2006;355:138–47.

41. Lindgren MP, Pirouzi-Fard M, Smith JG, Sundquist J, et al. Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. Science. 2000;290:1771–5.

42. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Europace. 2011;13:1077–109.

43. Ware JS, Cook SA. Role of titin in cardiomyopathy: from DNA variants to patient stratification. Nat Rev Cardiol. 2018;15:241–52.

44. Shah S, Henry A, Roselli C, et al. Genome-wide association and Mendelian randomisation analysis provide insights into the pathogenesis of heart failure. Nat Commun. 2020;11:163.

45. American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of medical care in diabetes-2020. Diabetes Care. 2020;43:S14–31.

46. Fadl HE, Simmons D. Trends in diabetes in pregnancy in Sweden 1998–2012. BMJ Open Diabetes Res Care. 2016;4:e000221.

47. Diabetes Prevention Program Research. G, Knowler WC, Fowler SE, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 2009;374:1677–86.
Ahlgqvist E, Storm P, Karjšakmaa A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol*. 2018;6:361–9.

Udler MS, Kim J, vonGrothuss M, et al. Type 2 diabetes genetic loci informed by multi-trait associations point to disease mechanisms and subtypes: A soft clustering analysis. *PloS Med*. 2018;15:e1002654.

Mahajan A, Wessel J, Willems SM, et al. Refining the accuracy of validated target identification through coding variant fine-mapping in type 2 diabetes. *Nat Genet*. 2018;50:559–71.

Dennis JM, Shields BM, Jones AG, Pearson ER, Hattersley AT, Henley WE, et al. Evaluating associations between the benefits and risks of drug therapy in type 2 diabetes: a joint modeling approach. *Clin Epidemiol*. 2018;10:1869–77.

Koivula RW, Forgie IM, Kurbasic A, et al. Assessment of the genetic and clinical determinants of fracture risk: genome wide association and Mendelian randomisation study. *BMJ*. 2018;362:k3225.

Morris JA, Kemp JP, Youlten SE, et al. An atlas of genetic influences on osteoporosis in humans and mice. *Nat Genet*. 2019;51:258–66.

Netzlander M, Pettersson-Kummer U, Vandepont L, Lorentz M, Karlsson M, Mellstrom D, et al. BMD-related genetic risk scores predict site-specific fractures as well as trabecular and cortical bone microstructure. *J Clin Endocrinol Metab*. 2020;105:e1344–e1357.

Forgetta V, Keller-Baruch J, Forest M, et al. Development of a polygenic risk score to improve screening for fracture risk: A genetic risk prediction study. *PloS Med*. 2020;17:e1003152.

Shepstone L, Lenaghan E, Cooper C, et al. Screening in the community to reduce fractures in older women (SCOOP): a randomised controlled trial. *Lancet*. 2018;391:741–7.

Makite RE, Costantini A, Kampe A, Alm JJ, Makite O. New insights into monogenic causes of osteoporosis. *Front Endocrinol (Lausanne)*. 2019;10:70.

Laine CM, Joeng KS, Campeau PM, et al. WNT1 mutations in early-onset osteoporosis and osteogenesis imperfecta. *N Engl J Med*. 2013;368:1809–16.

Topol EJ. A decade of digital medicine innovation. *Sci Transl Med*. 2019;11:eaaw7610.

Gustafsson M, Nestor CE, Zhang H, et al. Modules, networks and systems medicine for understanding disease and aiding diagnosis. *Genome Med*. 2014;6:82.

Shalek AK, Benson M. Single-cell analyses to tailor treatments. *Sci Transl Med*. 2017;9:eaan4730.

Gawel DR, Serra-Musach J, Lilja S, et al. A validated single-cell-based strategy to identify diagnostic and therapeutic targets in complex diseases. *Genome Med*. 2019;11:47.

Zhou X, Menche J, Barabasi AL, Sharma A. Human symptoms-disease network. *Nat Commun*. 2014;5:4212.

Ludvigsson JF, Almqvist C, Bonamy AK, et al. Registers of the Swedish total population and their use in medical research. *Eur J Epidemiol*. 2016;31:125–36.

Ludvigsson JF, Andersson E, Ekborn A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11:450.

Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekborn A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol*. 2009;24:659–67.

Esteve A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, et al. Dermatologist-level classification of skin cancer with deep neural networks. *Nature*. 2017;542:115–8.

McKinney SM, Sieniek M, Godbole V, et al. International evaluation of an AI system for breast cancer screening. *Nature*. 2020;577:89–94.

Henry KE, Hager DN, Pronovost PJ, Saria S. A targeted real-time early warning score (TREWScore) for septic shock. *Sci Transl Med*. 2015;7:299ra122.

Webb-Robertson BM, Bramer LM, Stanfill BA, et al. Prediction of the development of islet autoantibodies through integration of environmental, genetic, and metabolic markers. *J Diabetes*. 2021;13:143–53.

Koutsouleris N, Deyer DB, Degenhardt F, et al. Multimodal machine learning workflows for prediction of psychosis in patients with clinical high-risk syndromes and recent-onset depression. *JAMA Psychiatry*. 2020;78:195–209.

Corvin A, Craddock N, Sullivan PF. Genome-wide association studies: a primer. *Psychol Med*. 2010;40:1063–77.

Tam V, Patel N, Turcotte M, Bosse Y, Pare G, Meyre D. Benefits and limitations of genome-wide association studies. *Nat Rev Genet*. 2019;20:467–84.

Torkamani A, Wineinger NE, Topol EJ. The personal and clinical utility of polygenic risk scores. *Nat Rev Genet*. 2018;19:581–90.

van Dijk EL, Jaszczysyn Y, Naquin D, Thermes C. The Third Revolution in Sequencing Technology. *Trends Genet*. 2018;34:666–81.

Lappalainen T, Scott AJ, Brandt M, Hall IM. Genomic analysis in the age of human genome sequencing. *Cell*. 2019;177:70–84.

Jelin AC, Vora N. Whole exome sequencing: applications in genetic medicine. *Nat Rev Genet*. 2014;15:666–71.

El-Husseini ZW, Gosens R, Dekker F, et al. The personal and clinical utility of polygenic risk scores. *Nat Rev Genet*. 2018;19:581–90.

Nakagawa H, Fujita M. Whole genome sequencing analysis for cancer genomics and precision medicine. *Cancer Sci*. 2018;109:513–22.

Sanders SJ, Neale BM, Huang H, et al. Whole genome sequencing in psychiatric disorders: the WGS PD consortium. *Nat Neurosci*. 2017;20:1661–8.

Moll M, Sakornsakolpat P, Shrine N, et al. Chronic obstructive pulmonary disease and related phenotypes: polygenic risk scores in population-based and case-control cohorts. *Lancet Respir Med*. 2020;8:696–708.

El-Husseini ZW, Gosens R, Dekker F, Koppelman GH. The genetics of asthma and the promise of genomics-guided drug target discovery. *Lancet Respir Med*. 2020;8:1045–56.

Stengl R, Bors A, Agg B, et al. Optimising the mutation screening strategy in Marfan syndrome and identifying genotypes with more severe aortic involvement. *Orphanet J Rare Dis*. 2020;15:290.

Erbel R, Aboyans V, Boileau C, et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the
Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2014; 35: 2873–926.

86 Peters PT, Booij AC, van der Graaf F, Vader HL, Gerlag PG. Influence of low-dose acetylsalicylic acid on platelet function in patients on renal replacement therapy. Neth J Med. 1987;31:210–7.

87 Oresic M, Hyotylainen T, Kotronen A, et al. Prediction of non-alcoholic fatty-liver disease and liver fat content by serum molecular lipids. Diabetologia. 2013;56:2266–74.

88 Sazonov A, Kennedy NA, Moutsianas L, et al. HLA-DQA1*05 carriage associated with development of anti-drug antibodies to infliximab and adalimumab in patients with cromh’s disease. Gastroenterology. 2020;158:189–99.

89 Lee JC, Lyons PA, McKinney EF, et al. Gene expression profiling of CD8+ T cells predicts prognosis in patients with Crohn disease and ulcerative colitis. J Clin Invest. 2011;121:4170–9.

90 Biasci D, Lee JC, Noor NM, et al. A blood-based prognostic biomarker in IBD. Gut. 2019;68:1386–95.

91 Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, et al. Alzheimer’s disease. Lancet. 2016;388:505–17.

92 Strafella C, Caputo V, Galota MR, et al. Application of precision medicine in neurodegenerative diseases. Front Neurol. 2018;9:701.

93 Malik R, Chauhan G, Traylor M, et al. Multiancestry genome-wide association study of 520,000 subjects identifies 32 loci associated with stroke and stroke subtypes. Nat Genet. 2018;50:524–37.

94 Traylor M, Anderson CD, Rutten-Jacobs LCA, et al. Subtype specificity of genetic loci associated with stroke in 16 664 cases and 32 792 controls. Circ Genom Precis Med. 2019;12:e002338.

95 Kamitchum-Tatueue J, Jickling GC. Blood biomarkers for stroke diagnosis and management. Neuromolecular Med. 2019;21:344–68.

96 Abraham G, Malik R, Yonova-Doing E, et al. Genomic risk score offers predictive performance comparable to clinical risk factors for ischaemic stroke. Nat Commun. 2019;10:5819.

97 Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. Lancet. 2017;390:2673–734.

98 Goldman JS, Hahn SE, Catania JW, et al. Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. Genet Med. 2011;13:597–605.

99 Soderholm M, Pedersen A, Lorentzen E, et al. Genome-wide association meta-analysis of functional outcome after ischemic stroke. Neurology. 2019;92:e1271–e1283.

100 Mola-Caminal M, Carrera C, Soriano-Tarraga C, et al. PATJ low frequency variants are associated with worse ischemic stroke functional outcome. Circ Res. 2019;124:114–20.

101 Pfeiffer D, Chen B, Schlicht K, et al. Genetic imbalance is associated with functional outcome after ischemic stroke. Stroke. 2019;50:298–304.

102 Lo YM, Corbetta N, Chamberlain PF, Rai V, Sargent IL, Redman CW, et al. Presence of fetal DNA in maternal plasma and serum. Lancet. 1997;350:485–7.

103 Fan HC, Blumenfeld YJ, Chitkara U, Hudgins L, Quake SR. Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood. Proc Natl Acad Sci U S A. 2008;105:16266–71.

104 Bodurtha J, Strauss JP 3rd. Genomics and perinatal care. N Engl J Med. 2012;366:64–73.

105 Wastesson JW, Cedeo Mingoza A, Fastbom J, Maïlois S, Johnell K. The composition of polypharmacy: A register-based study of Swedes aged 75 years and older. PLoS One. 2018;13:e0194992.

106 Elliott LS, Henderson JC, Neradilek MB, Moyer NA, Ashcraft KC, Thurmarran RK. Clinical impact of pharmacogenetic profiling with a clinical decision support tool in polypharmacy home health patients: A prospective pilot randomized controlled trial. PLoS One. 2017;12:e0170905.

107 Gage BF, Bass AR, Lin H, et al. Effect of genotype-guided warfarin dosing on clinical events and anticoagulation control among patients undergoing hip or knee arthroplasty: The GIFT randomized clinical trial. JAMA. 2017;318:1115–24.

108 Bousman CA, Arandjelovic K, Mancuso SG, Eyre HA, Dunlop BW. Pharmacogenetic tests and depressive symptom remission: a meta-analysis of randomized controlled trials. Pharmacogenomics. 2019;20:37–47.

109 Tanner JA, Davies PE, Voudouris NC, et al. Combinatorial pharmacogenomics and improved patient outcomes in depression: Treatment by primary care physicians or psychiatrists. J Psychiatr Res. 2018;104:157–62.

110 Henricks LM, Lunenburg C, de Man FM, et al. DPYD genotype-guided dose individualisation of fluoropyrimidine therapy in patients with cancer: a prospective safety analysis. Lancet Oncol. 2018;19:1459–67.

111 Henricks LM, Lunenburg C, de Man FM, et al. A cost analysis of upfront DPYD genotype-guided dose individualisation in fluoropyrimidine-based anticancer therapy. Eur J Cancer. 2019;107:60–7.

112 He W, Grassmann F, Eriksson M, et al. CYP2D6 genotype predicts tamoxifen discontinuation and prognosis in patients with breast cancer. J Clin Oncol. 2020;38:548–57.

113 Cavallari LH, Lee CR, Beitelshees AL, et al. Multisite investigation of outcomes with implementation of CYP2C19 genotype-guided antplatelet therapy after percutaneous coronary intervention. JACC Cardiovasc Interv. 2018;11:181–91.

114 Srivastava S, Love-Nichols JA, Dies KA, et al. Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders. Genet Med. 2019;21:2413–21.

115 Sullivan PF, Owen MJ. Increasing the clinical psychiatric knowledge base about pathogenic copy number variation. Am J Psychiatry. 2020;177(3):204–9.

116 Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A. 2001;98:10869–74.

117 Easton DF, Pooley KA, Dunning AM, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature. 2007;447:1087–93.

118 Mavaddat N, Michailidou K, Dennis J, et al. Polygenic risk scores for prediction of breast cancer and breast cancer subtypes. Am J Hum Genet. 2019;104:21–34.
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119 Ronneild J, Hansson M, Mathsson-Alm L, et al. Anticitrullinated protein/peptide antibody multiplexing defines an extended group of ACNA-positive rheumatoid arthritis patients with distinct genetic and environmental determinants. Ann Rheum Dis. 2018; 77:203–11.

120 Han B, Diogo D, Eyre S, et al. Fine mapping seronegative and seropositive rheumatoid arthritis to shared and distinct HLA alleles by adjusting for the effects of heterogeneity. Am J Hum Genet. 2014;94:522–32.

121 Padyukov L, Seliestad M, Ong RT, et al. A genome-wide association study suggests contrasting associations in ACNA-positive versus ACNA-negative rheumatoid arthritis. Ann Rheum Dis. 2011; 70:259–65.

122 Pinart M, Benet M, Annesi-Maesano I, et al. Comorbidity of eczema, rhinitis, and asthma in IGE-sensitised and non-IGE-sensitised children in MeDALL: a population-based cohort study. Lancet Respir Med. 2014; 2:131–40.

123 van Beijsterveldt CE, Boomsma DI. Genetics of parentally reported asthma, eczema and rhinitis in 5-year-old twins. Eur Respir J. 2007; 29:816–21.

124 Ferreira MA, Vonk JM, Baurecht H, et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. Nat Genet. 2017; 49:1752–7.

125 Ferreira MAR, Vonk JM, Baurecht H, et al. Eleven loci with new reproductible genetic associations with allergic disease risk. J Allergy Clin Immunol. 2018; 19:012.

126 Lemonnier N, Melen E, Jiang Y, et al. A novel whole blood gene expression signature for asthma, dermatitis, and rhinitis multimorbidity in children and adolescents. Allergy. 2020; 75(12):3248–60.

127 Ludvigsson JF, Hemminki K, Wahlstrom J, Almqvist C. Celiac disease confers a 1.6-fold increased risk of asthma: A nationwide population-based cohort study. J Allergy Clin Immunol. 2011; 127:3–e4.

128 Metsala J, Lundqvist A, Virta LJ, Kaila M, Gissler M, Virtanen SM, et al. The association between asthma and type 1 diabetes: a paediatric case-cohort study in Finland, years 1981–2009. Int J Epidemiol. 2018; 47:409–16. https://doi.org/10.1093/ije/dyx245.

129 Demenais F, Margaritte-Jeannin P, Barnes KC, et al. Multiancestry association study identifies new asthma risk loci that colocalize with immune-cell enhancer marks. Nat Genet. 2018; 50:42–53.

130 Mogensen N, Larsson H, Lundholm C, Almqvist C. Association between childhood asthma and ADHD symptoms in adolescence - a prospective population-based twin study. Allergy. 2011; 66:1224–30.

131 Holmberg K, Lundholm C, Anckarsater H, Larsson H, Almqvist C. Impact of asthma medication and familial factors on the association between childhood asthma and attention-deficit/hyperactivity disorder: a combined twin- and register-based study: Epidemiology of Allergic Disease. Clin Exp All. 2015; 45:964–73.

132 Cortese S, Sun S, Zhang J, et al. Association between attention deficit hyperactivity disorder and asthma: a systematic review and meta-analysis and a Swedish population-based study. Lancet Psychiatry. 2018; 24:30224–4.

133 Brew BK, Lundholm C, Gong T, Larsson H, Almqvist C. The familial aggregation of atopic diseases and depression or anxiety in children. Clin Exp All. 2018; 7:13127.

134 Ferreira MAR, Mathur R, Vonk JM, et al. Genetic architectures of childhood- and adult-onset asthma are partly distinct. Am J Hum Genet. 2019; 104:665–84. https://doi.org/10.1016/j.ajhg.2019.02.022.

135 Dijk FN, Folkersma C, Gruzieva O, et al. Genetic risk scores do not improve asthma prediction in childhood. J Allergy Clin Immunol. 2019; 144(3):857–860.e7.

136 Melen E, Guerra S, Hallberg J, Jarvis D, Stanojevic S. Linking COPD epidemiology with pediatric asthma care: Implications for the patient and the physician. Pediatr Allergy Immunol. 2019; 30:589–97.

137 Bisgaard H, Stokholm J, Chawes BL, et al. Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring. N Engl J Med. 2016; 375:2530–9.

138 de Lange KM, Moutsianas L, Lee JC, et al. Genome-wide association study implicates immune activation of multiple integrin genes in inflammatory bowel disease. Nat Genet. 2017; 49:256–61.

139 Mirko MU, Verstockt B, Cleynen I. Genetics of inflammatory bowel disease: beyond NOD2. Lancet Gastroenterol Hepatol. 2017; 2:224–34.

140 Uhlig HH, Schwed T, Koletzko S, et al. The diagnostic approach to monogenic very early onset inflammatory bowel disease. Gastroenterology. 2014; 147(5):990–1007.e3.

141 Relling MV, Schwab M, Whirl-Carrillo M, et al. Clinical pharmacogenetics implementation consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. Clin Pharmacol Ther. 2019; 105:1095–105.

142 Walker GJ, Harrison JW, Heap GA, et al. Association of genetic variants in NUDT15 with thiopurine-induced myelo-suppression in patients with inflammatory bowel disease. JAMA. 2019; 321:773–85.

143 Heap GA, Weedon MN, Bewshea CM, et al. HLA-DQA1-HLA-DRB1 variants confer susceptibility to pancreatitis induced by thiopurine immunosuppressants. Nat Genet. 2014; 46:1131–4.

144 Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016; 64:73–84.

145 Hagstrom H, Naser P, Ekstedt M, Hammar U, Stal P, Hultcrantz R, et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. J Hepatol. 2017; 67:1265–73.

146 Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA. 2015; 313:2263–73.

147 Mayo R, Crespo J, Martinez-Arranz I, et al. Metabolomic-based noninvasive serum test to diagnose nonalcoholic steatohepatitis: Results from discovery and validation cohorts. Hepatol Commun. 2018; 2:807–20.

148 Barr J, Caballeria J, Martinez-Arranz I, et al. Obesity-dependent metabolic signatures associated with nonalcoholic fatty liver disease progression. J Proteome Res. 2012; 11:2521–32.

149 Luukkonen PK, Zhou Y, Sadevirta S, et al. Hepatic ceramides dissociate steatosis and insulin resistance in patients with non-alcoholic fatty liver disease. J Hepatol. 2016; 64:1167–75.

150 Abu-Husn NS, Cheng X, Li AH, et al. A protein-truncating HSD17B13 variant and protection from chronic liver disease. N Engl J Med. 2018; 378:1096–106.

151 Hardy T, Wonders K, Younes R, et al. The European NAFLD Registry: A real-world longitudinal cohort study of
nonalcoholic fatty liver disease. *Contemp Clin Trials*. 2020;**98**:106175.

152 Masoodi M, Gastaldelli A, Hyötyläinen T, et al. Metabolomics and Lipidomics in NASH: from identifying biomarkers to the development of non-invasive diagnostic tests. *Nat Rev Gastroenterol Hepatol*. 2021. in press.

153 Liu CC, Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurosci*. 2013;**9**:106–18.

154 Lambert JC, Ibrahim-Verbaas CA, Harold D, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer’s disease. *Nat Genet*. 2013;**45**:1452–8.

155 Stocker H, Möllers T, Perna L, Brenner H. The genetic risk of Alzheimer’s disease beyond APOE e4: a systematic review of Alzheimer’s genetic risk scores. *Transl Psychiat*. 2018;**8**:166.

156 Logue MW, Panizzon MS, Elman JA, et al. Use of an Alzheimer’s disease polygenic risk score to identify mild cognitive impairment in adults in their 50s. *Mol Psychiatry*. 2019;**24**:421–30.

157 Lambert SA, Abraham G, Inouye M. Towards clinical utility of polygenic risk scores. *Hum Mol Genet*. 2019;**28**:R133–R142.

158 Leonenko G, Sims R, Shoaí M, et al. Polygenic risk and hazard scores for Alzheimer’s disease prediction. *Ann Clin Transl Neurol*. 2019;**6**:456–65.

159 Ryan L, Huy M, Huentelman MJ, et al. Precision Aging: applying precision medicine to the field of aging. *Front Aging Neurosci*. 2019;**11**:128.

160 Poewe W, Seppi K, Tanner CM, et al. Parkinson disease. *Nat Rev Dis Primers*. 2017;**3**:17013.

161 Kalia LV, Lang AE. Parkinson’s disease. *Lancet*. 2015;**386**:896–912.

162 Nalls MA, Pankratz N, Lill CM, et al. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson’s disease. *Nat Genet*. 2014;**46**:989–93.

163 Chang D, Nalls MA, Hallgrímsdóttir IB, et al. A meta-analysis of genome-wide association studies identifies 17 new Parkinson’s disease risk loci. *Nat Genet*. 2017;**49**:1511–6.

164 Mejeini R, Flynn LL, Pitout IL, Fletcher S, Wilton SD, Akkari PA. ALS genetics, mechanisms, and therapeutics: where are we now? *Front Neurol*. 2019;**10**:1310.

165 Olszewska DA, Lonergan R, Fallon EM, Lynch T. Genetics of frontotemporal dementia. *Curr Neurol Neurosci Rep*. 2016;**16**:107.

166 Ferrari R, Hernandez DG, Nalls MA, et al. Frontotemporal dementia and its subtypes: a genome-wide association study. *Lancet Neurol*. 2014;**13**:686–99.

167 Piehl F, Kockum I, Khademi M, Blennow K, Lycke J, Zetterberg H, et al. Plasma neurofilament light chain levels in patients with MS switching from injectable therapies to fingolimod. *Mult Scler*. 2018;**24**:1046–54.

168 Hakansson I, Tinell A, Cassel P, et al. Neurofilament light chain in cerebrospinal fluid and prediction of disease activity in clinically isolated syndrome and relapsing-remitting multiple sclerosis. *Eur J Neurol*. 2017;**24**:703–12.

169 Giovannoni G, Butzkueven H, Dhib-Jalbut S, et al. Brain health: time matters in multiple sclerosis. *Mult Scler Relat Disord*. 2016;**9**(Suppl 1):S5–S48.

170 International Multiple Sclerosis Genetics C. Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. *Science*. 2019;**365**:eaav7188.

171 Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. *Nat Rev Neurol*. 2017;**13**:25–36.

172 Noseworthy JH, Barkhof F, Natalizumab. *Nat Rev Drug Discov*. 2005;**4**:101–2.

173 Sundqvist E, Buck D, Warnač C, et al. JC polyomavirus infection is strongly controlled by human leucocyte antigen class II variants. *PLoS Pathog*. 2014;**10**:e1004064.

174 Pedersen A, Jern C. Heritability of ischemic stroke and intracerebral hemorrhage. In: Seshadri S, Debette S, editors. *Risk factors for cerebrovascular disease and stroke*. Oxford, UK: Oxford University Press Inc.; 2016. pp. 64–74.

175 Rutten-Jacobs LC, Larsson SC, Malik R, et al. Genetic risk, incident stroke, and the benefits of adhering to a healthy lifestyle: cohort study of 306 473 UK Biobank participants. *BMJ*. 2018;**363**:k4168.

176 Jickling GC, Kittern SJ. A SNP-it of stroke outcome. *Neurology*. 2019;**92**:549–50.

177 Tan KY, Markus HS. Monogenic causes of stroke: now and the future. *J Neurol*. 2015;**262**:2601–16.

178 Norton ME, Jacobsson B, Swaný G, et al. Cell-free DNA analysis for noninvasive examination of trisomy. *N Engl J Med*. 2015;**372**:1589–97.

179 Warrington NM, Beaumont RN, Horikoshi M, et al. Maternal and fetal genetic effects on birth weight and their relevance to cardio-metabolic risk factors. *Nat Genet*. 2019;**51**:804–14.

180 Zhang G, Feenstra B, Bacelis J, et al. Genetic associations with gestational duration and spontaneous preterm birth. *N Engl J Med*. 2017;**377**:1156–67.

181 McGinnis R, Steinthorsdottir V, Williams NO, et al. Variants in the fetal genome near FLT1 are associated with risk of preeclampsia. *Nat Genet*. 2017;**49**:1255–60.

182 Huusko JM, Karjalainen MK, Graham BE, et al. Whole exome sequencing reveals HSPA1L as a genetic risk factor for spontaneous preterm birth. *PLoS Genet*. 2018;**14**:e1007394.

183 Ferrero DM, Larson J, Jacobsson B, et al. Cross-country individual participant analysis of 4.1 million singleton births in 5 countries with very high human development index confirms known associations but provides no biologic explanation for 2/3 of all preterm births. *PLoS One*. 2016;**11**:e0162506.

184 Rheinbay E, Nielsen MM, Abascal F, et al. Analyses of non-coding somatic drivers in 2,658 cancer whole genomes. *Nature*. 2020;**578**:102–11.

185 Consortium IT-P-CaWG. Pan-cancer analysis of whole genomes. *Nature*. 2020;**578**:82–93.

186 Nik-Zainal S, Davies H, Stafa J, et al. Landscape of somatic mutations in 560 breast cancer whole-genome sequences. *Nature*. 2016;**534**:47–54.

187 Ding L, Ley TJ, Larson DE, et al. Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing. *Nature*. 2012;**481**:506–10.

188 Puente XS, Finny M, Quesada V, et al. Whole-genome sequencing identifies recurrent mutations in chronic lymphocytic leukaemia. *Nature*. 2011;**475**:101–5.

189 Zehir A, Benayed R, Shah RH, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. *Nat Med*. 2017;**23**:703–13.
190 He J, Abdel-Wahab O, Nahas MK, et al. Integrated genomic DNA/RNA profiling of hematologic malignancies in the clinical setting. Blood. 2016;127:3004–14.

191 Genomic Medicine Sweden. GMS and Illumina collaborate to develop whole-genome sequencing for patients with acute leukemia. Available at https://genomicmedicine.se/en/2020/05/28/gms-illumina-whole-genome-sequencing-acute-leukemia/. 2020 May 28.

192 Genomic Medicine Sweden. Childhood cancer. 2021. Available at https://genomicmedicine.se/en/childhood-cancer/.

193 van der Velden DL, Hoes LR, van der Wijngaart H, et al. The Drug Rediscovery protocol facilitates the expanded use of existing anticancer drugs. Nature. 2019;574:127–31.

194 Horak P, Klink B, Heining C, et al. Precision oncology based on omics data: The NCT Heidelberg experience. Int J Cancer. 2017;141:877–86.

195 Zhang H, Ahearne TU, Lecarpentier J, et al. Genome-wide association study identifies 32 novel breast cancer susceptibility loci from overall and subtype-specific analyses. Nat Genet. 2020;52:572–81.

196 Law PJ, Timofrova M, Fernandez-Rozadilla C, et al. Association analyses identify 31 new risk loci for colorectal cancer susceptibility. Nat Commun. 2019;10:2154.

197 Speedy HE, Di Bernardo MC, Sava GP, et al. A genome-wide association study identifies multiple susceptibility loci for chronic lymphocytic leukemia. Nat Genet. 2014;46:56–60.

198 Milne RL, Antoniou AC. Modifiers of breast and ovarian cancer risks for BRCA1 and BRCA2 mutation carriers. Endocr Relat Cancer. 2016;23:769–84.

199 Couch FJ, Wang X, McGuffog L, et al. Genome-wide association study in BRCA1 mutation carriers identifies novel loci associated with breast and ovarian cancer risk. PLoS Genet. 2013;9:e1003212.

200 Johnell K, Fasthomb J. Comparison of prescription drug use between community-dwelling and institutionalized elderly in Sweden. Drugs Aging. 2012;29:751–8.

201 Tinetti ME. The gap between clinical trials and the real world: extrapolating treatment effects from younger to older adults. JAMA Intern Med. 2014;174:397–8.

202 Reeve E, Wiese MD, Mangoni AA. Alterations in drug disposition in older adults. Expert Opin Drug Metab Toxicol. 2015;11:491–508.

203 Hallberg P, Collin S, Wadelius ML. Preventivt arbete kan minska l

204 Golebski K, Kabesch M, Melen E, et al. Childhood asthma in the new omics era: challenges and perspectives. Curr Opin Allergy Clin Immunol. 2020;20:155–61.