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JIM Review

doi: 10.1111/joim.13330

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].

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/trig/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]

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.

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

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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 alpha$_1$-antitrypsin (AAT) deficiency [19]. AAT deficiency is most commonly caused by homozygosity for the *SERPINA1***Z* 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,

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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, whereas in many complex diseases, GDPM has little or no proven 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

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Journal of Internal Medicine, 2021; 290: 602–620

Table 2 *Complex diseases and examples of GDPM applications*

	Evidence of technological readiness (emphasis on the feasibility of genomic or precision medicine)							
Medical area	Diagnostic Classification	Example	Disease prevention	Example	Disease treatment	Example	Disease prognosis	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].	Poor		Moderate	Genomics-guided drug discovery and repurposing of existing drugs for **asthma** are promising [83]. However, the clinical benefit of such approach is yet to be proven.	None	
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	
			Excellent	Genetically diagnosed connective tissue syndromes (e.g. Marfan's syndrome) have specific thresholds for preventive **aortic** surgery [84,85].				
Endo-crinology	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 PRS is currently being evaluated in **osteoporosis**, but it may improve screening by identifying a subset	None		None	

Table 2 (*Continued*)

	Evidence of technological readiness (emphasis on the feasibility of genomic or precision medicine)							
Medical area	Diagnostic Classification	Example	Disease prevention	Example	Disease treatment	Example	Disease prognosis	Example
		Finnish cohorts [49], with widespread replication. Similar studies have been performed using genetic classification [50] [86].		of high-risk individuals who might particularly benefit from osteoporosis therapy [56,57].				
Gastro-enterology	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	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 patters 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].
	Moderate	Pharmacogenetic studies investigating genetic variants in genes coding for dopaminergic receptors show individual fluctuations in response to administration of L-						

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Table 2 (*Continued*)

	Evidence of technological readiness (emphasis on the feasibility of genomic or precision medicine)							
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.
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	Pharmacogenetic profiling is a feasible way to improve prognosis in ageing patients. Examples: Genotyping predicts tamoxifen discontinuation

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Table 2 (*Continued*)

	Evidence of technological readiness (emphasis on the feasibility of genomic or precision medicine)							
Medical area	Diagnostic Classification	Example	Disease prevention	Example	Disease treatment	Example	Disease prognosis	Example
				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].		and prognosis in women with breast cancer [112]. 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].
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	
	Good	1–3% of adults with severe psychotic disorders will have a pathogenic copy number variants [115]						
Oncology – example breast cancer	Good	The first paper on molecular subtyping of breast cancer was published in 2001 [116]. Since then, thousands of papers have been published on the subject and molecular subtypes, as prognosticators, are now part of clinical	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		Poor	

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Table 2 (*Continued*)

	Evidence of technological readiness (emphasis on the feasibility of genomic or precision medicine)							
Medical area	Diagnostic Classification	Example	Disease prevention	Example	Disease treatment	Example	Disease prognosis	Example
		practice in the Western world. Slowly emerging are molecular profiles with a therapy predictive implication; however, these markers are far from clinical practice.		(NEJM 2021, in press). The first five SNPs linked to breast cancer were described in 2007 [117]. Today, an additional ≈300 SNPs are associated with the risk of breast cancer and the polygenic risk score is constantly growing [118]. Many of the genetic determinants of breast cancer are, however, yet to be identified.				
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.	Moderate	There is evidence for a more severe disease phenotype of SLE amongst patients with a high genetic risk score [18].

COPD, Chronic obstructive pulmonary disease; GRS, genomic risk score; IBD, inflammatory bowel disease; NAFLD, non-alcoholic fatty liver disease; SLE, systemic lupus erythematosus.

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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 monogenetic 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

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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

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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,

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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 (Vetenskapsrådet, 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.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. An update of genomic-driven precision medicine efforts across major areas of medicine.

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