Special Report

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Pharmacogenomics

Pharmacogenomics education, research and clinical implementation in the state of Minnesota

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Several healthcare organizations across Minnesota have developed formal pharmacogenomic (PGx) clinical programs to increase drug safety and effectiveness. Healthcare professional and student education is strong and there are multiple opportunities in the state for learners to gain workforce skills and develop advanced competency in PGx. Implementation planning is occurring at several organizations and others have incorporated structured utilization of PGx into routine workflows. Laboratory-based and transla-

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tional PGx research in Minnesota has driven important discoveries in several therapeutic areas. This article reviews the state of PGx activities in Minnesota including educational programs, research, national consortia involvement, technology, clinical implementation and utilization and reimbursement, and outlines the challenges and opportunities in equitable implementation of these advances.

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Healthcare in Minnesota

Minnesota (MN) is home to more than 5.6 million people. A large majority (79%) of the state's present population is non-Hispanic White [1], mainly of German and Norwegian descent [2]. MN's non-white population is comprised of 7.0% African Americans, 5.6% Latinx, 5.2% Asian, 1.4% American Indian and 0.1% Native Hawaiian and other Pacific Islanders [1]. MN is increasing in diversity and by 2053 the population of color is projected to reach 2.4 million [3]. Notably, MN has the largest Somali (n = 65,379) and second-largest Hmong (n = 81,966) [4–6] populations in USA. Foreign-born residents are 8.5% of the state's population, with immigrants and refugees arriving from Mexico, Southeast Asia, Ethiopia, Korea, Liberia, Burma and Bhutan [7]. The Twin Cities (St. Paul, Minneapolis and suburbs) comprise ~55% of the state's population; other urban areas account for ~18% while 8% of Minnesota's population lives in more remote rural areas [8]. The state's demographics underscore the need for deliberate approaches that embrace diversity when implementing pharmacogenomics (PGx).

MN has a strong managed healthcare history and led the nation in creating Pharmacy Benefit Managers. It also has a robust health insurance exchange (MNsure), with available coverage options that are low-cost (MinnesotaCare) or free (Medical Assistance), and private insurance plans with and without financial assistance. The distribution of MN's primary source of insurance coverage in 2017 was private (58%), Medicare (17.4%), Medical Assistance or MinnesotaCare (17.3%), Department of Defense Military Health System and TRICARE (1.1%); 6.3% were uninsured [9]. Despite having a strong marketplace, MN has some of the greatest health disparities in the country between whites and non-white population.

As a percentage of total healthcare spending, MN has greater spending coming from private insurance and higher medical assistance than the rest of the USA. MN spends a greater percentage of healthcare dollars on long-term care and retail prescription drugs than the rest of the USA. In 2014, retail sales of prescription drugs in MN amounted to $3.76 billion [10]. Between 2009 and 2013, pharmacy and medical prescription drug spending totaled $33.4 billion arising from 369.6 million claims [10]. The five therapeutic categories with the largest pharmacy drug claims spending in 2013 were endocrine and metabolic, cardiovascular, central nervous system, analgesics and anesthetics and respiratory medications [11]. Prevalence of prescribed medications with an actionable PGx association is high in MN. A recent analysis of the MN All Claims Payer Database showed that more than 6.2 million prescriptions – costing USD$ 241 million – were written for CPIC level A drugs in 2016 [12,13]. These data show that a significant number of individuals are exposed to medications for which genetic information might have been useful in optimizing therapy.

Several healthcare organizations across MN have developed PGx programs or use PGx testing to improve health outcomes through increased drug safety and effectiveness. PGx is well developed at three large healthcare organizations in the state, while many other health systems are implementing, planning implementation or have structured utilization programs to incorporate PGx into routine workflows. This article discusses the status of PGx in MN, including educational programs, research, consortia involvement, PGx technology and implementation, utilization and reimbursement and outlines the challenges and opportunities in equitable implementation of these advances.

Pharmacogenomics education

Professional & graduate education

The University of Minnesota (UMN) College of Pharmacy has provided PGx education to Doctor of Pharmacy (PharmD) and graduate students since 2011. UMN genetic counseling, public health and health informatics programs have introduced PGx content into their curricula. In the PharmD program, PGx content is integrated across pharmacotherapy courses and an advanced PGx elective. In 2021, all incoming PharmD students will have

Table 1. Recurring formal clinical pharmacogenomics workforce education resources in the state of Minnesota.

Institution	Description	Website
Mayo Clinic	Pharmacogenomics for your practice	https://ce.mayo.edu/online-education/content/pharmacogenomics-your-practice----online
	Center for Individualizing Medicine (CIM) Conference	https://individualizingmedicineconference.mayo.edu
OneOme	OneOme Institute	https://www.oneome.com/institute/
Sanford Health	Sanford Imagenetics Genomic Medicine Symposium and Lecture Series	https://imagenetics.sanfordhealth.org/community/
University of Minnesota	Precision Medicine and/or PGx Conferences	http://mpmc.umn.edu/news/conferences
	Precision Medicine and PGx Seminar	http://mpmc.umn.edu/precision-medicine-seminar-series
Sanford Health	Sanford Imagenetics Genomic Medicine Symposium	https://imagenetics.sanfordhealth.org/community/

the opportunity to receive PGx testing, and the results will be used longitudinally in educational activities. PharmD students enrolled in the research emphasis track have opportunities to conduct PGx research with faculty advisors in areas from discovery to policy. Summer research programs and advanced pharmacy practice experiences in PGx and internships at commercial PGx companies are available to students. UMN College of Pharmacy also offers PGx-focused MS and PhD programs. Mayo Clinic Alix School of Medicine has coursework embedded into the first-year pharmacology curriculum for medical students. Additionally, a 1-week elective is offered to medical students to explore individualized medicine applications.

Postgraduate PharmD programs

There are two PGx postgraduate year 2 residency programs for pharmacists in MN – one at Mayo Clinic and one at Children's Minnesota – with a third to launch at Sanford Health. PGx residencies are relatively new in the field of pharmacy and those in MN are among only a few programs across the nation that are developing this clinical training. Several PGx-related fellowship programs exist in MN that focus on clinically oriented research, which necessitates prior clinical training. The PGx fellowship program at Essentia Health in Duluth, MN, is a partnership between a rural health system and the UMN College of Pharmacy and focuses on PGx implementation. The Psychopharmacology and Pharmacogenomics Fellowship at the UMN College of Pharmacy contains clinical PGx and laboratory genetics training in mental health in collaboration with Genoa Healthcare. Mayo Clinic hosts a National Institutes of Health T32 Clinical Pharmacology Fellowship that educates MD, DO, PharmD and PhD trainees at the convergence of genomics and pharmacology.

Workforce education

Workforce education, concentrated in PGx continuing education (CE) and national conference opportunities for healthcare professionals, has been a focus for the UMN College of Pharmacy (Table 1) and for various organizations implementing PGx.

The Mayo Clinic Center for Individualized Medicine (CIM) education program was created in 2012 to provide resources for translating PGx into practice. CIM has developed integrated approaches to educate clinicians and researchers through an annual precision medicine conference that provides CE and includes both scientific and clinical genomic medicine content. In 2020, CIM launched a certificate program, Pharmacogenomics For Your Practice [14], that offers physicians, pharmacists and nurses opportunities to obtain education in clinical PGx topics and to earn CE.

UMN has hosted a national PGx-oriented CE-bearing Precision Medicine Conference every other year since 2016. This live conference in Minneapolis (virtual in 2020) has grown from a 1-day event focusing on PGx discovery to a 2-day meeting that provides PGx clinical and implementation education and optional personal PGx testing (Table 1). To disseminate knowledge widely, the UMN conference is open to the public. UMN has also organized PGx-themed education during its annual mini-medical school, where the public is informed through lectures and one-on-one interactions with professionals.

Sanford Health has emphasized developing provider education and support resources to increase clinician confidence in PGx during the launch of their precision prevention initiative in 2012. Ongoing education and support interventions include required computer-based training modules, increasing access to genetics specialists, and clinical decision support capabilities. These strategies are complemented by a repository of online and print resources, and the annual Sanford Imagenetics Genomic Medicine Symposium that offers CE.

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OneOme, an MN-based commercial PGx testing company, provides education and support for PGx integration to healthcare professionals through the OneOme Institute. This includes customized training programs on basic science principles and clinical PGx. OneOme offers webinars, educational blogs and educational PGx testing to complement collaborative conferences and CE programs (e.g., with UMN and Mayo Clinic).

Pharmacogenomics research

MN is unique in its combination of academic and clinically oriented research activities related to PGx that span multiple therapeutic areas and both public and private institutions. As Tier 1 research institutions, UMN and Mayo Clinic are engaged in laboratory-based, translational and clinical research. UMN has its Advanced Pathways to Research Program (A-PreP), a summer immersion experience for doctoral-level health sciences professional students. Other health systems (including Children's Minnesota, Allina Health, Essentia Health and HealthPartners) have research institutes that support their clinical missions. While it is not feasible to enumerate all of the active PGx projects within the state, examples below highlight the breadth and depth of ongoing research.

Discovery

Discovery-based PGx research is strong at the major academic institutions in MN, such as UMN and Mayo Clinic. One of the earliest PGx discoveries came from MN researchers who identified variation in the *TPMT* gene and the increased risk for toxicity and potentially deadly exposures to 6-MP and azathioprine [15]. These discoveries revolutionized thiopurine dosing and influenced the broader field of PGx. Mayo Clinic has significantly contributed to understanding the importance of *DPYD* and *CYP2D6* genetic variation for 5-fluorouracil [16–18] and tamoxifen [19–21], respectively. Subsequent discovery research has examined relationships between genetic variability in the *CYP3A* genes, differences in genetic variation across populations, and its impact in patients treated with tacrolimus [22–26] and other immunosuppressants. These genetic studies were used to develop PGx-driven dosing models. Researchers in MN have developed novel computational methods to estimate treatment response in clinical cancer genomics data sets. The models link gene expression to drug response in cancer cell lines, which are then associated with somatic variants that identify predictive biomarkers for cancer drugs [27]. The discovery of unique pharmaco-alleles found at high frequency within underserved populations has implications regarding drug selection, dosing and development of PGx assays. Such is the case for Minnesota Hmong compared with non-Hmong Asian populations, underscoring the importance of deliberate inclusion and ensuring access to appropriate genetic testing to avoid exacerbating health disparities in implementation of PGx [28,29].

Optimizing treatments for mental health is a growing area for PGx applications. The first genome-wide discovery study of antipsychotic treatment response in persons experiencing their first episode of psychosis was published by a MN-led research team [29]. This work established that neurotransmitter systems beyond known pharmacodynamic targets of antipsychotics may impact response. Investigational approaches for depression are now integrating PGx with computational informatics including artificial intelligence to predict which drugs will work best for patients with known and unknown genetic and clinical characteristics [30]. Ongoing studies are using next-generation sequencing to identify novel variants of drug metabolizing genes such as *CYP2C19* [30] and *CYP2D6* in understudied communities such as the Hmong [31].

Laboratory methods

The close juxtaposition of academic and commercial labs in the state creates a productive environment for the development of laboratory methods. Laboratories have traditionally used targeted genotyping-based methods to interrogate variation. Next-generation sequencing approaches are an emerging alternative but have limitations in characterizing certain pharmacogenes and raise concerns about how to classify rare variants. MN researchers have advanced both the analysis and clinical application of next-generation sequencing data. These contributions include discerning reliable assignment of hypersensitivity (human leukocyte antigen [HLA]) genes [32] and drug metabolism variants such as *CYP2C9* and *CYP2C19* with next-generation sequencing, and developing strategies to characterize and act on variants of uncertain significance.

Implementation

Three large implementation-focused research efforts are underway in MN: the UMN Grand Challenge Minnesota Precision Medicine Collaborative, the Mayo Clinic Right 10 K study, and MN involvement in the Electronic Medical Records and Genomics (eMERGE) Network. To our knowledge, the UMN-supported 'Grand Challenge

– Implementing Pharmacogenomics at a State-Wide Scale' project is a one-of-a-kind implementation effort supporting foundational work to advance PGx utilization and research across an entire state. Through this work, a multi-organization PGx clinical decision support (CDS) and a statewide data shelter are being designed. Individuals with PGx testing results or with new orders for testing may consent to archiving their PGx results so that they are accessible across MN health systems to avoid retesting and, if the patient agrees, made available for research.

The RIGHT10K project is an ongoing collaboration among Mayo Clinic, Baylor College of Medicine and OneOme in which 11,000 individuals have undergone sequencing-based testing for 84 pharmacogenes with entry of 12 of these into the EHR [33]. The study aims to determine the clinical implications of variants of uncertain significance identified through sequencing, whether pre-emptive PGx testing improves outcomes and reduces costs, and how clinician and patient perceptions of care are affected.

eMERGE-PGx was a targeted sequencing study supported by NIH to assess variation in 82 pharmacogenes and to integrate information into the EHR [34]. Essentia Health and Mayo Clinic, along with others in the nation, enrolled ~5000 participants. eMERGE-PGx identified a median of two actionable PGx variants per person, with more than 1800 individuals having three or more actionable variants. Extrapolating this to national prescription information suggested ~75 million prescriptions in the USA could be affected each year by knowing genetic variation.

Minnesota representation in national consortia

MN has long exercised leadership and contributed to national and international precision medicine consortia. The Clinical Pharmacogenetics Implementation Consortium (CPIC) is an NIH-supported group which creates expert consensus guidelines on how to consider PGx in clinical care. Of the 400 international members of this group, 29 are from MN, with members from Mayo Clinic, Sanford, Essentia Health, UMN, Children's MN, OneOme, Goodrich Pharmacy and others. MN authors have contributed to approximately one third of the guidelines for medications used in cardiology, infectious diseases, mental health, oncology and pain.

The NIH-supported Implementing Genomics In Practice (IGNITE) consortium was created to advance the use of genomic medicine by developing methods to incorporate genomic information into care and to support implementation, diffusion and sustainability. IGNITE comprises seven funded sites and 17 affiliate institutions including Sanford, UMN, Essentia Health and OneOme. UMN has contributed to IGNITE PGx working group projects characterizing successful workflows, institutional processes and implementation assessments of antidepressant PGx programs. UMN has also contributed to projects identifying opportunities and barriers to the implementation of PGx for drugs metabolized by CYP2D6 [35] and the assessment of PGx in pediatrics. Sanford is a site for a Depression and Opioid Pragmatic Trial in Pharmacogenetics.

MN institutions are also involved in the All of Us Research Program, the largest NIH-funded precision medicine initiative in USA. It is a nationally coordinated research effort seeking to improve the way disease is treated and prevented through whole genome sequencing of at least one million volunteers. Essentia Health is the primary site recruiting participants from MN, North Dakota and Wisconsin. HealthPartners in Minneapolis also began recruitment in 2020. Mayo Clinic houses the All of Us program's DNA BioBank and supports the collection, analysis, storage and distribution of the samples.

Other national and international consortia with MN representation include the Pharmacogene Variation Consortium [36], the Pharmacogenomics Research Network and the Standardizing Laboratory Practices in Pharmacogenomics collaborative forum.

Pharmacogenomics technology development & laboratory testing

Numerous hospital-based and commercial laboratories are located in MN and provide PGx testing services. These laboratories offer testing for variants in individual genes, but the trend is to offer comprehensive PGx panels.

The Personalized Genomics Laboratory at Mayo Clinic is the longest-standing PGx testing lab in MN, having established services in 2003 with analysis of *CYP2D6*. The lab expanded to include additional single genes until advances in multiplexing technology allowed for the launch of low-cost panels in 2017. The commercial companies, Assurex (now part of Myriad; mental-health focused), OneOme (broad therapeutic applications) and Geneticure (hypertension) all can trace intellectual origins or contributions from experts at Mayo Clinic (Table 2). Sanford Medical Genetics Laboratory is located in Sioux Falls, SD, but supports PGx testing in all of Sanford's MN clinics and hospitals and provides PGx testing in rural practices. The newest laboratory launching an in-house

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Table 2. Laboratories in Minnesota providing clinical pharmacogenomic testing.

Lab name	Therapeutic area focus	Genes tested
Assurex Health (now Myriad Neuroscience)†	Mental health	*CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, HLA-A*31:01, HLA-B*15:02, HTR2A, SLC6A4, UGT1A4, UGT2B15*
Geneticure	Hypertension	*ACE, ADD1, ADRB1, ADRB2, AGT, AGTR1, CYP2D6, REN, SCNN1A, SLC12A3, WNK1*
Mayo Clinic	Various	*ADRA2A, ANKK1, CHRNA3, COMT, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, CYP4F2, CYP2C cluster, DPYD, DRD2, EPHX1, F2, F5, G6PD, GRIK4, HLA-A*31:01, HLA-B*15:02, HLA-B*57:01, HLA-B*58:01, HTR2A, HTR2C, IL28B (IFNL3), MTHFR, NAT2, NUDT15, OPRM1, SCN1A, SLC6A4, SLCO1B1, TPMT, UGT1A1, UGT2B15, VKORC1*
Sanford Health	Various	*CYP2C Cluster, CYP2C9, CYP2C19, CYP2D6, CYP3A5, CYP4F2, DPYD, IFNL3, SLCO1B1, TPMT, VKORC1*
OneOme	Various	*COMT, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, CYP2C Cluster, CYP4F2, DPYD, DRD2, F2, F5, GRIK4, HLA-A*31:01, HLA-B*15:02, HLA-B*57:01, HLA-B*58:01, HTR2A, HTR2C, IFNL4, NUDT15, OPRM1, SLC6A4, SLCO1B1, TPMT, UGT1A1, VKORC1*
M Health Fairview	Various	*CYP2D6, CYP3A5, CYP2B6, CYP2C9, TPMT, SLCO1B1, CYP2C19, DPYD, UGT1A1*

†Assurex originated in Minnesota.

comprehensive panel assay is the MHealth Fairview Molecular Diagnostics Laboratory. It is implementing the custom-built reporting CDS software tool ('Go4PGx') developed within the UMN Grand Challenge Initiative.

Clinical implementation & utilization of pharmacogenomics

Clinical PGx testing and use in MN fall into four general categories: formalized implementation programs within specific health organizations; structured utilization and/or ordering within health organizations, pharmacy-facilitated utilization in the community and utilization by individual providers or small provider groups separate from categories 1–3. Sanford Health, Mayo Clinic and Children's MN have formal PGx programs, with a program at M Health Fairview launched in 2021. PGx in other organizations is at different stages of transitioning to formalized implementation. MN is unique in this regard, because many other states have only one (if any) large institution with a structured program. With multiple established programs, including pediatric specialty care and many other health systems heading in this direction, MN has a diversity of urban and rural environments now embracing PGx implementation. As a national leader in community pharmacy-based comprehensive medication management, MN has extensive pharmacy involvement in facilitating PGx implementation.

Implementation programs within specific health systems

Mayo Clinic was the first health system in MN to integrate PGx into clinical programs. CIM garnered institutional support in 2012 to establish the infrastructure for one of the nation's most recognized PGx programs. Mayo Clinic has ascertained and deposited preemptive and reactive PGx test results in the EHR [37], using laboratory tests done on site and those by commercial labs. Best practice alerts provide recommendations linked to AskMayoExpert, an online resource, for 23 drug/gene pairs (Table 3) at the point-of-prescribing. Pharmacists at Mayo Clinic provide consults though a pharmacist-run PGx clinic.

Sanford Imagenetics was established in 2014. Sanford Imagenetics' multidisciplinary approach has integrated medical groups to form a genetic medicine program, of which PGx integration in primary care is a prioritized component [38]. Imagenetics first implemented PGx testing in 2015 with *CYP2C19* testing for clopidogrel. An eight-gene pre-emptive panel was introduced in 2016. In 2020, additional genes were added to the panel (see Table 3 for current gene list), which captures most drug–gene interactions deemed actionable by CPIC. CDS provides best practice alerts to inform providers of drug–gene interactions and recommend alternatives. Most testing utilizes the 'Sanford Chip' that contains both PGx and disease risk markers, although individual gene tests are also available [39].

Children's MN established their PGx program in 2016 and is one of only a few pediatric specialty organizations in the country with formalized PGx implementation. Custom CDS delivers PGx test results for 11 genes and 28 medications (Table 3) using commercial laboratories for testing. Results are interpreted by PGx pharmacists for application to younger patients. A PGx clinic and consult service takes referrals, offers standardized test ordering, provides interpretation and recommendations, and returns results to providers and patients. A multidisciplinary group is involved in these genomic medicine activities, although the PGx program is primarily led by pharmacists.

Table 3. Drug–gene pairs implemented at Minnesota pharmacogenomics programs.

Drug	Gene	Mayo Clinic	Children's MN	Sanford Health	M Health Fairview	CPIC level of evidence[†]
Abacavir	*HLA-B*	X	X			A
Allopurinol	*HLA-B*	X	X			A
Amitriptyline	*CYP2C19*		X	X	X	A
Amitriptyline	*CYP2D6*		X	X	X	A
Aripiprazole	*CYP2D6*		X			B
Atazanavir	*UGT1A1*		X			A
Atomoxetine	*CYP2D6*		X	X	X	A
Azathioprine	*TPMT*	X	X	X	X	A
Azathioprine	*NUDT15*	X	X			A
Belinostat	*UGT1A1*	X				B
Capecitabine	*DPYD*	X	X	X		A
Carbamazepine	*HLA-A*	X	X			A
Carbamazepine	*HLA-B*	X	X			A
Celecoxib	*CYP2C9*			X	X	A
Citalopram	*CYP2C19*	X	X	X	X	A
Clomipramine	*CYP2C19*		X	X	X	B
Clomipramine	*CYP2D6*		X	X	X	B
Clopidogrel	*CYP2C19*	X	X	X	X	A
Codeine	*CYP2D6*	X	X	X	X	A
Desipramine	*CYP2D6*		X	X	X	B
Doxepin	*CYP2D6*		X	X	X	B
Doxepin	*CYP2C19*		X	X	X	B
Efavirenz	*CYP2B6*		X		X	A
Escitalopram	*CYP2C19*	X	X	X	X	A
Fluorouracil	*DPYD*	X	X	X	X	A
Fluoxetine	*CYP2D6*	X				C
Flurbiprofen	*CYP2C9*			X		A
Fluvoxamine	*CYP2D6*	X	X	X	X	B
Ibuprofen	*CYP2C9*			X	X	A
Imipramine	*CYP2C19*		X	X	X	B
Imipramine	*CYP2D6*		X	X	X	B
Irinotecan	*UGT1A1*	X	X			A
Meloxicam	*CYP2C9*			X	X	A
Mercaptopurine	*TPMT*	X	X	X		A
Mercaptopurine	*NUDT15*	X	X			A
Nortriptyline	*CYP2D6*		X	X	X	A
Ondansetron	*CYP2D6*		X	X	X	A
Oxcarbazepine	*HLA-A*	X				C
Oxcarbazepine	*HLA-B*	X				A
Paroxetine	*CYP2D6*	X	X	X	X	A
Peginterferon alfa-2a	*IFNL3*			X		A
Phenytoin	*CYP2C9*		X	X		A
Phenytoin	*HLA-B*		X			A
Rasburicase	*G6PD*					A
Sertraline	*CYP2C19*		X	X	X	B
Simvastatin	*SLCO1B1*	X	X	X	X	A
Tacrolimus	*CYP3A5*	X	X	X	X	A
Tamoxifen	*CYP2D6*	X			X	A

[†]CPIC evidence levels as of 13 May 2021.

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Table 3. Drug–gene pairs implemented at Minnesota pharmacogenomics programs (cont.).

Drug	Gene	Mayo Clinic	Children's MN	Sanford Health	M Health Fairview	CPIC level of evidence†
Tenoxicam	*CYP2C9*			X	X	A
Thioguanine	*TPMT*	X	X	X		A
Thioguanine	*NUDT15*	X	X			A
Tramadol	*CYP2D6*	X	X	X	X	A
Trimipramine	*CYP2C19*		X	X	X	B
Trimipramine	*CYP2D6*		X	X	X	B
Venlafaxine	*CYP2D6*	X	X			A/B
Voriconazole	*CYP2C19*		X	X	X	A
Warfarin	*CYP2C9*	X	X	X		A
Warfarin	*CYP4F2*			X		A
Warfarin	*VKORC1*	X		X		A

†CPIC evidence levels as of 13 May 2021.

Structured utilization of PGx within health systems or institutions

Additional health systems have recognized the importance of incorporating PGx into care delivery and are developing procedures for test ordering, workflow, EHR integration with and without CDS and PGx services. M Health Fairview is an example, implementing a PGx testing program across selected inpatient services and clinics starting in 2021. The program is driven by a collaboration among the Molecular Diagnostics Laboratory, UMN Department of Laboratory Medicine and Pathology, Fairview Pharmacy, UMN Institute of Health Informatics and UMN College of Pharmacy. The in-house multiplexed genotyping assay detects variants in 11 CPIC guideline-supported genes, with more genes assays in development (Table 3). The program is implementing reactive testing, with the long-term goal being pre-emptive testing.

Essentia Health, Allina Health, HealthPartners (and likely others) are in the early stages of developing structured PGx utilization and eventually full implementation programs. One common theme across institutions implementing PGx is that they are first adding structure to the ordering procedures for commercial PGx tests, with processes to track who has received testing and from which lab. Another common theme is the engagement of pharmacists to lead implementation. All health facilities have identified challenges in committing personnel time and budgets for developing CDS, differing inpatient versus outpatient workflows, workforce education, reimbursement and decisions regarding using commercial labs versus developing in-house assays.

Pharmacist-facilitated utilization

For non-hospital and ambulatory settings, there are a growing number (10+) of pharmacy-based programs facilitating patient access to PGx testing. These are mostly independently owned or small-chain community pharmacies with connections to medical clinics, and tend to be serving defined communities (e.g., in smaller cities) or connected to community behavioral health clinics. Pharmacists with PGx expertise serve as the primary resource at these locations. The pharmacies facilitate testing broadly in two ways, by having the pharmacist discuss testing with the patient who has a prescription, or by responding to a direct inquiry from the patient. In either scenario a test may be ordered by a pharmacist under a collaborative practice agreement or ordered by a patient's provider after a pharmacist recommendation. The pharmacists then receive and interpret the results for the patient and provider.

Utilization by individual providers or small provider groups

This last category of PGx utilization is common albeit difficult to quantify as it represents individual providers or provider groups that order testing directly from commercial laboratories. These results are then available to the specific providers linked to the results portal.

Utilization of PGx medications, testing & reimbursement

Uncertainties in estimating test utilization and revenue are common implementation challenges. Numbers of test orders in the state are difficult to establish, but inquiries with local commercial and institutional laboratories (see Table 2) provide rough estimates of trends. Data for orders that originated in MN suggested that in 2019, nearly

10,000 tests were ordered in MN from a single out-of-state commercial lab. Other data suggest that the number of PGx test orders has increased up to 250% in the past 5 years (2014–2019) for some labs.

Reimbursement trends in MN appear to vary by test and year, with reimbursement occurring only for some of the PGx tests. In USA, PGx testing is covered by Medicare in some regions through Local Coverage Determinations made by the Medicare Administrative Contractor (MAC) for that region. The MAC that processes claims for MN, National Government Services, does not currently have a Local Coverage Determination for reimbursement of PGx tests. This presents a challenge for implementation efforts in the state. Other MACs have coverage policies for *CYP2D6*, *CYP2C19*, *CYP2C9*, *HLA-B*15:02*, *HLA-A*31:01*, multi-gene panels and combinatorial PGx tests.

Challenges & opportunities in Minnesota

MN faces challenges in translating decades of PGx discoveries to clinical care beyond large healthcare organizations. However, the state possesses a unique assembly of healthcare organizations that are forward thinking and committed to equitably improving medication and health outcomes. This creates opportunities for change, but certain actions are needed to facilitate sustainability in our state: dedicated education on the value of PGx to the healthcare workforce, commercial and CMS payers, and self-insured employers; education of patients about potential implications that PGx may have on their drug therapies and improving how they access and share their testing results with providers; employing trained pharmacists to assess patient needs for PGx testing, order tests and recommend or make appropriate changes in therapy; state legislative support for equitable deployment of PGx across MN to underrepresented groups through a state task force and grants program; addressing the challenges in access to PGx testing and lack of qualified professionals to interpret results in settings that serve rural, minority and indigenous people; educing the burdens of implementing PGx at smaller, rural, and underserved healthcare organizations by developing shareable PGx knowledge-based tools and software to increase utilization and improve outcomes; and addressing inequities in payer reimbursements for PGx testing.

Conclusion & future perspectives

MN has numerous strengths in PGx. These include many educational opportunities for professional and graduate students as well as established healthcare professionals, a diverse body of research across the translational spectrum, business development, and representation on national consortia. Clinical PGx programs are established at some institutions, but there are barriers that limit widespread implementation. A statewide Grand Challenge Research Initiative supported by the UMN aims to advance PGx utilization and education, and to make PGx more accessible to rural and underrepresented populations. Next steps will include: developing a community of PGx practice that collaborates to build knowledge and skills; creating a shareable statewide CDS system to facilitate equitable access to evidence-based resources and accurate interpretation of results; building a structure to allow portability of clinical PGx results to reduce unnecessary retesting; training health professionals to deliver patient and provider education; and the development of a data shelter to support future discovery PGx research. Collectively these next steps align with a broad vision for PGx in MN to make evidence-based testing and educational resources accessible to those who need them, and that this will be supported by a knowledgebase that continues to be informed by collaborative research and professional connectivity across the state.

Summary points

- Minnesota (MN) has a strong history of pharmacogenomic (PGx) education, research contributions, consortia representation and PGx practice and business development.
- Active clinical implementation efforts in a variety of practice environments are notable strengths, but widespread and equitable use in clinical practice outside of larger institutions has lagged.
- MN has high prescription drug expenditures with many of those having actionable PGx markers, suggesting that the implementation of PGx may have a high impact in the state. Focused efforts are needed by healthcare organizations, payers and the state legislature to integrate PGx into the standard of care where appropriate to improve treatment outcomes.

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Author contributions

JR Bishop and PA Jacobson generated the concept for the manuscript, all authors provided input in the organization and content to be included and contributed information or writing to be included. JR Bishop led the writing of the manuscript and all authors contributed to the writing or content. All authors approved of the final version submitted.

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