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1. Executive Summary

The present white paper represents a vision of the state-wide deployment of PGx in the state of Minnesota. We discuss:

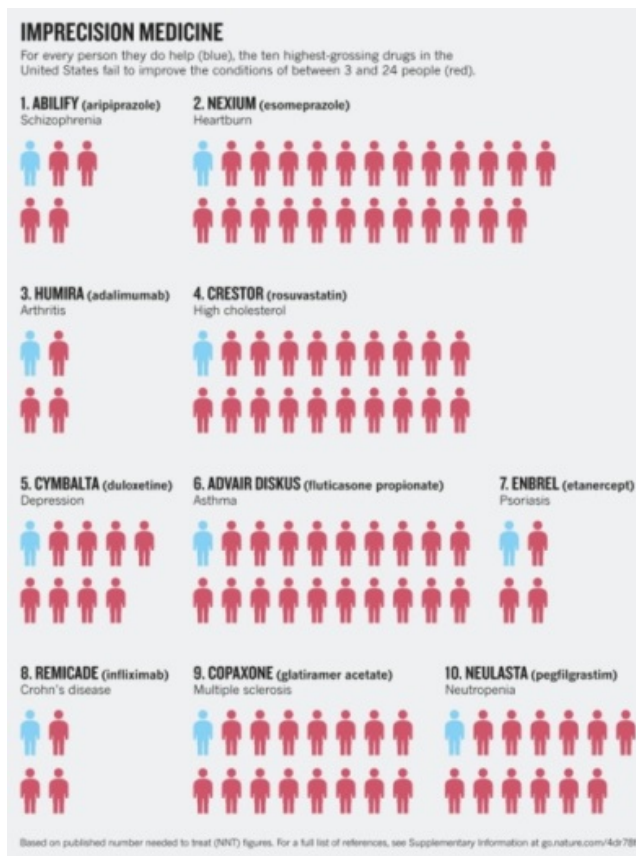
- What is Pharmacogenomics (PGx)?
- Examples of vivid and compelling case studies that can be communicated in plain language to the citizens of MN to garner broadest support possible.
- The case studies also showcase:
 - Why is PGx important for improving medication efficacy?
 - Why is PGx important for improving medication safety?
 - Why is PGx important for reducing medication and overall healthcare costs?
- Beneficiaries of PGx.
- Pillars of PGx.
- A blueprint for PGx development across the state.

2. Pharmacogenomics (PGx): The Science of “The Right Drug For You”

In a shocking 2015 report published in the medical journal *Nature*, the top ten grossing medications in the US were reported to fail to improve the intended disease condition in most patients (Nature 30 April 2015; 520; 609).

For example, only 1 of 4 patients have improvement with Abilify and only 1 of 25 patients improve with Nexium (**Figure to right**).

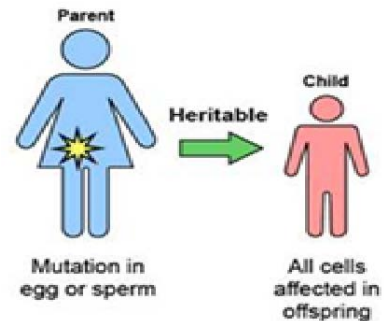
The failure and rising cost of ineffective drug therapies has had significant consequences on our health care costs. According to the Office of the Actuary in the Centers for Medicare & Medicaid Services, prescription drug expenditures from all payers (private health insurance, Medicare, Medicaid, others) are projected to grow from \$311.9 billion in 2017 to \$527.5 billion in 2025. The projected



growth is unsustainable and requires a multi-pronged approach to improve the delivery of highly effective therapy while responsibly reducing costs.

One powerful and scientifically well-studied and sound approach to addressing this nationwide problem is the implementation of one form of precision medicine – pharmacogenomics.

Pharmacogenomics matches an individual’s genetic makeup with medications. Individuals inherit genes (also referred to as alleles) from their parents that have variations (also called mutations or variants) creating a completely unique individual (**Figure to right**). Each person has their own unique ability to respond to medications and eliminate them from the body. Genes that cause medications to have slow or no elimination from the body can result in serious toxicities or other side effects. Other genes may influence one’s response to a medication. In the last 20 years, much has been learned about medications and genes through research. The science is now sufficiently mature for implementation into care.



3. Case Studies of How Pharmacogenomics Can Save Lives, Improve Well-being and Reduce healthcare Costs.

The cases below are stories of individuals with medical conditions that have benefited or would have benefited from knowledge of their genetics through testing and education of the provider in how to use that knowledge.

3.1. Case Study #1: Finding the Right Anti-Depressant

This is a representative case study of how medicines may cause in patients adverse effects with dire implications in their well-being, ability to work and ability to stay on the medication for the long term. The consequences are dire for both patients, employers, and the ever increasing costs of our healthcare system. The case described here is perfectly feasible today with existing PGx science and technology. The vision for the future is the wide-spread of the existing PGx capabilities.

Patricia is a 23-year old female with a history of depression from age of 16. She has had several trials of the SSRIs and TCAs antidepressant medications but has not remained on these medications due to them causing fatigue, drowsiness and blurry vision which affected her abilities at work. She has also had multiple absences from work due to the illness and medical appointments caused by these medications.

Vision for the future: Patricia’s company recently transferred her to MN for work. MN has a widely deployed PGx system in place where everyone is tested for PGx variants and the results are stored so that when a medication is prescribed the prescribing clinician is immediately alerted if the drug is likely to not work.

Patricia's new primary care doctor would like to restart her on anti-depressant therapy but given her side effect history she first obtains the pharmacogenomics test panel results and requests automatically generated medication alerts for Patricia. She finds that Patricia carries a genetic variant in the CYP2D6 gene which places her at high risk of anti-depressant side effects. Her CYP2C19 gene testing did not detect mutations. Her doctor reviews the list of proposed alternative drugs proposed by the PGx system and prescribes a new antidepressant that is not affected by these variants. Patricia remains side-effect free at 1 year after starting this new therapy and she has had improvement in her depression symptoms.

3.2. Case Study #2: Failure of Cardiovascular Therapy Leading to a Second Heart Attack

This is a representative case study of how medicines that protect against critical medical events may fail to function in certain patients. The consequences are dire for both patients, employers, and the ever increasing costs of our healthcare system. The case described here is perfectly feasible today with existing PGx science and technology. The vision for the future is the wide-spread of the existing PGx capabilities.

Janice is a 68 year old, 59 kg female, admitted to the emergency department after an episode of sustained chest pain that radiated down her left arm. She is diagnosed with ST-segment elevation myocardial infarction (heart attack). A percutaneous coronary intervention is performed (balloon catheter threaded into the obstructed artery and inflated to relieve the narrowing). She is discharged from the hospital with the anti-platelet drug clopidogrel 75 mg daily and aspirin 325 mg daily. This drug has a critical role: it helps prevent the formation of new blood clots in the narrowed artery and subsequent new heart attacks and thus is life-saving when working as intended.

Four weeks after the discharge, however Janice returns back to the emergency department with chest pain and is found to have a 2nd myocardial infarction.

Vision for the future: Janice, like every MN state resident, is genetically tested for all known PGx variants. The MN PGx alerting system generates an alert triggered by the angioplasty procedure, that informs the provider team that Janice has genetic alleles (CYP2C19*2/*3, which occur in 2-15% of patients) that prevent the activation of clopidogrel and therefore this drug is not effective for her. Several alternative drugs are proposed by the system and on the basis of this test, Janice is given a different antiplatelet drug that is not affected by these alleles and thus a second heart attack is avoided.

3.3. Case Study #3: Gout and a Life-Threatening Medication Adverse Effect

This is a representative case study of how medicines may cause life-threatening reactions to patients and how such hyper-sensitivities are more common in patients of specific racial/genetic backgrounds. The case described here is perfectly feasible today with existing PGx science and technology. The vision for the future is the wide-spread of the existing PGx capabilities.

Will is a 41 year old previously healthy Chinese-American male who develops excruciating pain and swelling in his right big toe. His primary care doctor diagnoses him with gout, provides treatment, and the symptoms are gone within 48 hours. Will has 3 other flares of his gout over the next year. Due to the frequency of his gout attacks, he is placed on allopurinol 300 mg once daily to prevent future attacks. Two weeks after beginning allopurinol, he notices a rash on his abdomen. The following day the rash has spread to his chest and arms. By the time Will visits his doctor the rash has begun to blister and spread to other sites of his body. His allopurinol is immediately stopped. Will is diagnosed with a serious drug hypersensitivity reaction, Steven Johnson Syndrome, which kills 1 in 4 patients it affects. The severity of his rash progresses and he is admitted to the hospital and is eventually transferred to the intensive care unit. Will is in serious risk of dying due to this drug-induced condition.

Vision for the future: Will, like every MN state resident, is genetically tested for all known PGx variants. Will’s test reveals that he carries the HLA-B*5801 allele which is highly associated with allopurinol drug hypersensitivity. About 3-10% of individual’s of Chinese ancestry will carry this allele. The MN PGx system alerts his physician to not administer allopurinol and provide alternative gout treatment thus preventing a life-threatening complication.

4. Beneficiaries of PGx.

Table 1 shows the many beneficiaries and the many benefits of PGx

<i>Beneficiary</i>	<i>Type of benefit</i>
Patients/health services consumers	<ul style="list-style-type: none"> • Eliminate/reduce avoidable adverse drug events • Increase medication efficacy • Select the right dose • Reduce time to find the right drug (compared to trial-and-error approaches of today) • Increase adherence to therapeutic regimes since side effects are reduced • Decrease loss of work days and increase overall productive time • Increase overall well-being
Providers	<ul style="list-style-type: none"> • Increase quality of care by avoiding adverse drug events, by finding most effective drugs and most effective doses • Decrease costs due to avoidable adverse drug events, non compliance to medication • Increase re-imbursements by providing better care through avoidance of adverse drug events and improving outcomes
Payers	<ul style="list-style-type: none"> • Decrease costs of care and payments for delayed effective care, and for avoidable adverse events and other dire outcomes
Biotech industry	<ul style="list-style-type: none"> • Create the next generation of PGx test panels to cover more drugs and more patient cohorts
Pharma industry	<ul style="list-style-type: none"> • Avoid costly litigation resulting from adverse events • Reduce risk or drug withdrawals for toxicity or ineffectiveness • Reduce risk for Clinical Trial failures
Employers	<ul style="list-style-type: none"> • Increase well-being and productivity of employees • Reduce costs of employee insurance

State	<ul style="list-style-type: none"> • Increase well-being of state citizens and residents • Increase productivity, reduce costs of care • Lead the nation in PGx policy, deployment, education, and R&D • New product opportunities for biotech and pharma (to be marketed nationwide and internationally)
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5. Pillars of Large-Scale PGx.

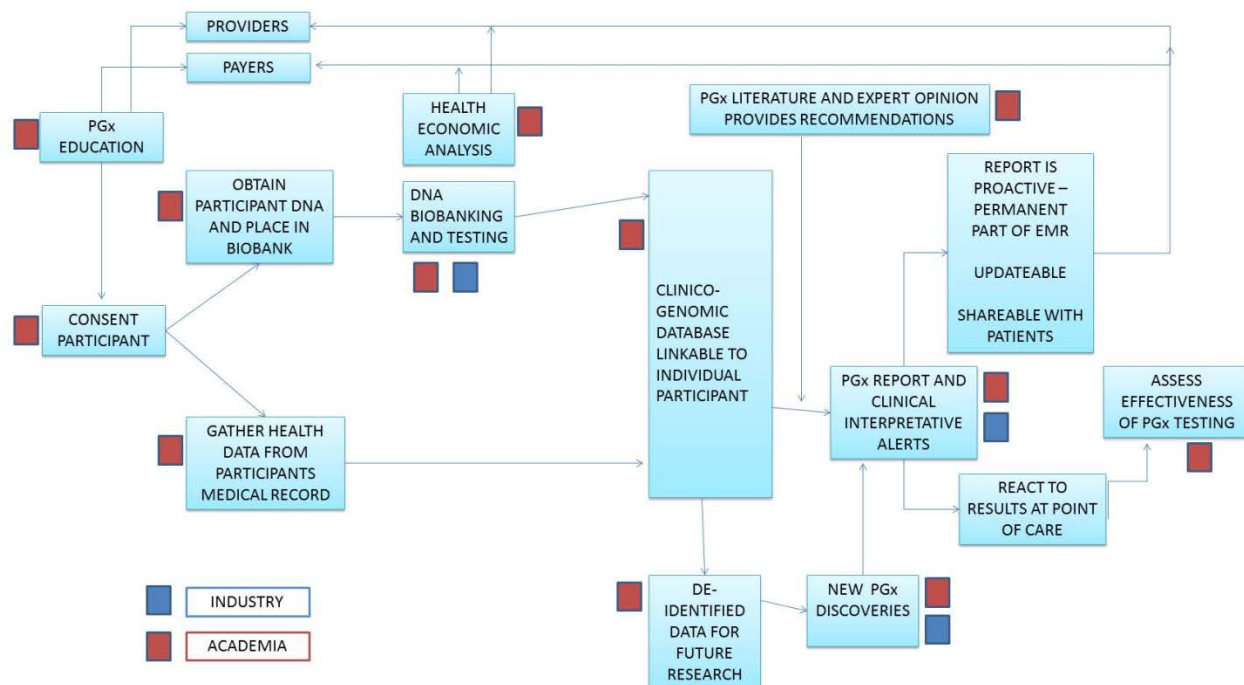
Table 2 shows the necessary ingredients (“Pillars”) for large-scale deployment of PGx in the state of MN that creates an environment for immediate deployment of known PGx variants, discovery of new variants and creation of a state precision medicine powered health care systems.

<i>Table 2. Ingredients needed for PGx</i>	
<i>PGx Pillar</i>	<i>Actions</i>
Policy	<ul style="list-style-type: none"> • Create a roadmap and policy framework for deployment of PGx • Specify opportunities, aspirations, tangible/measurable results, incentives and funding • Enhance human subjects protection over the current standard of federal law (to ensure that any type of possible abuse of genetic information will be illegal) • Create a phased deployment plan starting from state employees to full-state coverage
Science	<ul style="list-style-type: none"> • Develop and implement systems for evidence-driven clinical interpretation of PGx variants at point of care • Discover new actionable variants • Integration of clinical + PGx information for mining/modeling for optimized care • Develop cost effective methods for PGx testing
Technology	<ul style="list-style-type: none"> • Focused (e.g., targeted) and high-throughput (e.g., whole exome) genetic testing • Develop clinical information system integration for decision support at the point of care at doctor’s offices and pharmacies • Data security measures to ensure that abuse of genetic information will be technically impossible
Education	<ul style="list-style-type: none"> • Educate policy makers • Educate citizens, parents, healthcare consumers • Educate practitioners • Educate underserved and minority populations, and populations disproportionately affected by PGx-preventable conditions
Health Economics	<ul style="list-style-type: none"> • Establish value/ROI of PGx deployment at full scale and at targeted scale for every stakeholder • Establish short, mid and long term amortization of PGx investments
Stakeholders and	<ul style="list-style-type: none"> • Patients/health services consumers

stakeholder engagement	<ul style="list-style-type: none"> • Providers • Payers • Biotech industry • Employers • State groups • Pharmaceutical industry
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6. A blueprint for PGx development across the state.

Figure 3 depicts the interplay of activities in a fully-deployed state-wide PGx framework. The figure also shows the roles that various participants and stake holders may play.



As the figure shows, the new elements over existing infrastructure include: (a) **PGx educational programs and resources** for patients, providers (clinicians and administrators) and payers (administrators). The educational modalities will vary in sophistication and depth according to the audience. (b) **DNA testing and biobanking** facilities. (c) A **Clinico-Genomic data base** which captures data from the Electronic medical record (EMR) data extraction and linkage with genetic data into 2 databases: a virtualized genomic medical record and a de-identified derivative for research and R&D, (d) A creation of **PGx reports and interpretative alerts** through a clinical evidence review panel informing decision making. The interpretation will become part of the medical record, will be communicated with the patients and will be used for generation of point-of-care alerts when providers prescribe (or are likely to prescribe) drugs affected by actionable PGx variants. (e) **Research and R&D** functions both at academic and industry sites

for creation, validation and deployment of next generation of PGx tests. (f) **Health economic analysis** for use by providers, payers and industry to deploy cost-effective PGx.

With red color we outline functions that can be undertaken by academic entities and by blue industry (Biotech+Pharma. Providers and Payer's functions are not included in the annotation).