Personalized Medicine

The Medicine of the Future is Happening Now

pmi Personalized Medicine Initiative

a place of mind UBC Life Sciences Institute

Forces Driving Personalized Medicine

1) Rapid technological change (inexpensive molecular level analyses)
2) Patient safety (adverse drug reactions)
3) Drug efficacy (50% of drugs don't work on the person they are prescribed for)
4) Consumer demand (individualized, effective, non-toxic treatment)
5) Preventive medicine (need individualized, definitive data)

A tsunami of change is hitting the medical system

Patient Safety: Adverse Drug Reactions Are the Fourth Leading Cause of Death in North America

Cause of death	Number of deaths
Heart disease	743,460
Cancer	529,904
Stroke	150,108
Adverse drug reactions	106,000 (range 76,000-137,000)
Pulmonary disease	101,077
Accidents	90,523
Pneumonia	75,523
Diabetes	53,894

90% of adverse drug reactions are not reported

Drug Efficacy: More Than 50% of Drugs Do Not Work on the Patient They are Prescribed For

Drug		Efficacy
Anti-Depressants	62 %	
Asthma	60 %	
Diabetes	57 %	
Arthritis	50 %	
Alzheimer	30 %	
Cancer	25 %	

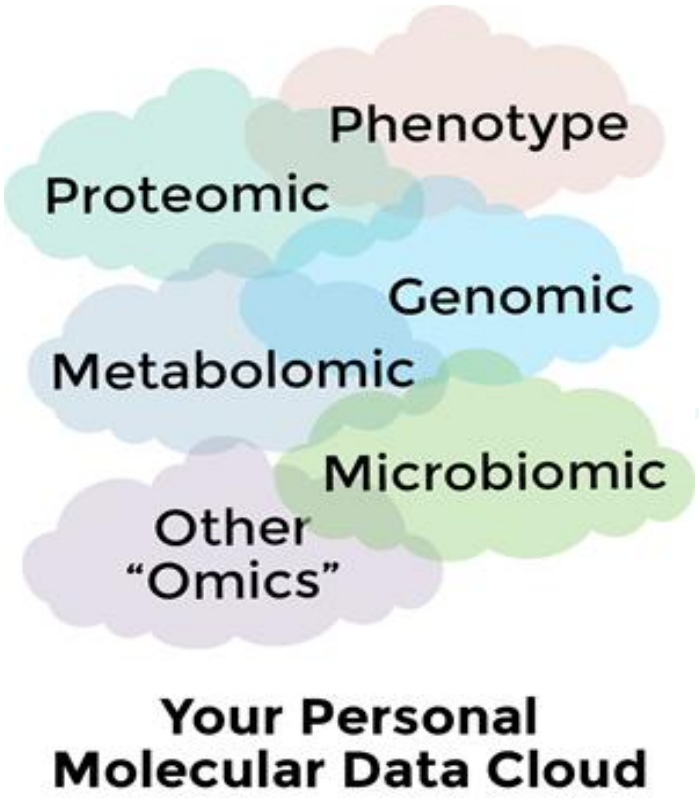

Drug does not work

These Issues Arise Due To "One Size Fits All" Healthcare

The problem is, we are all different!

Personalized Medicine: Healthcare Based On The Molecular Makeup Of The Individual And Their Disease

Molecular "Omic" Analyses



Benefits

- Early detection of disease
- More effective and safer therapeutics
- More effective preventive medicine
- More efficient healthcare

Many Companies/Initiatives Being Formed to Implement Personalized Medicine

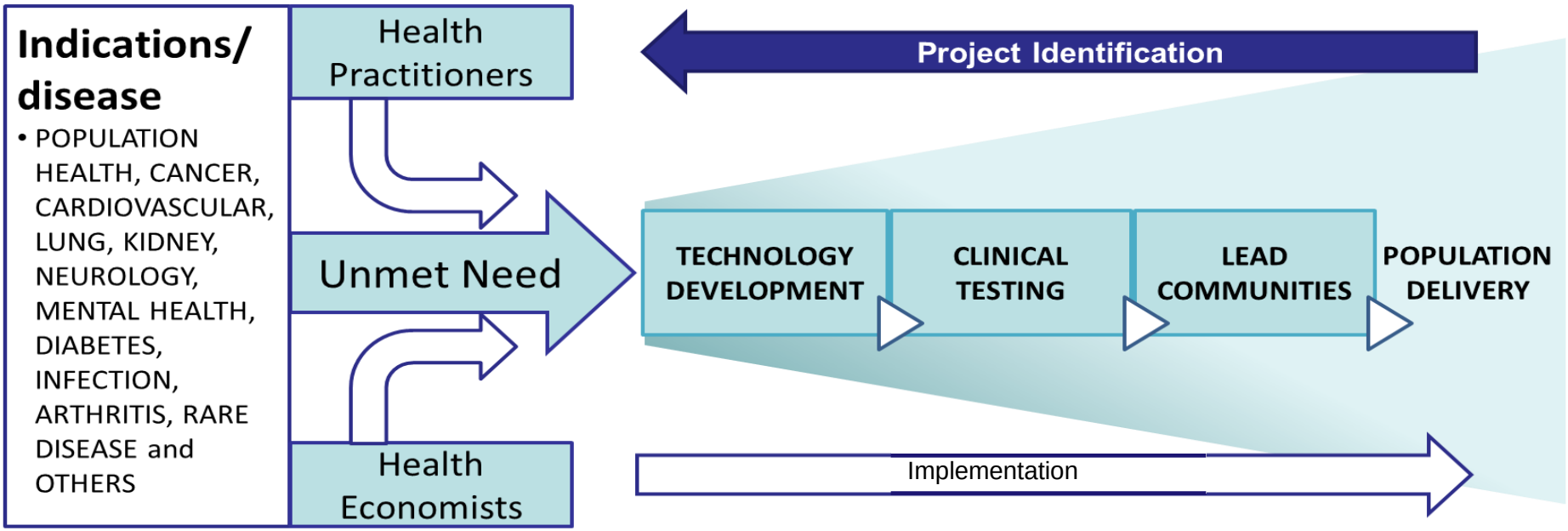
- Genome England (100,000 genomes project)
- Precision Medicine Initiative (USA)
- Human Longevity Inc. ($300M raised, tackling the diseases of aging)
- Calico (Google spinout, aging)
- 23&me, Genova Diagnostics, Color (ovarian cancer), ParasitologyX3 (stool), μbiome, Great Plains Lab, Cleveland Heart……
- **Personalized Medicine Initiative (Canada)**

The Personalized Medicine Initiative

Vision: Introduce **into the population** an individualized approach to healthcare based on the molecular makeup of the individual and their disease

What the PMI does

Prioritizes disease & preventive care opportunities, sources funding for them, implements and commercializes



The PMI plays a driving, hands-on role to implement molecularly based medicine into the front lines of healthcare

The PMI is Tightly Coupled With Clinical, Life Science and Natural Science Resources in BC

pmi Projects

- Implementation projects
- Outreach projects
- Infrastructure projects
- New companies

The PMI Has Developed a "Roadmap for Bringing Personalized Medicine to the Population"* in BC

Recommendations:

1. Encourage a political/public commitment to personalized medicine (2% of healthcare budget)
2. Establish coalition of healthcare, academic, industry & patients to promote personalized medicine
3. **Take advantage of near-term opportunities for implementation of personalized medicine**
4. Construct a patient-centred clinical database for 25,000 Canadians

*see http://personalizedmedicineinitiative.ca/

Implementation of Personalized Medicine Requires Molecular Profiling and Clinical Decision Support Systems

Molecular profiling:

- Genomic, proteomic, metabolomic, microbiomic analyses
- The PMI has formed **Molecular You Corp.** to provide Omic data clouds and interpretation (diagnose disease)

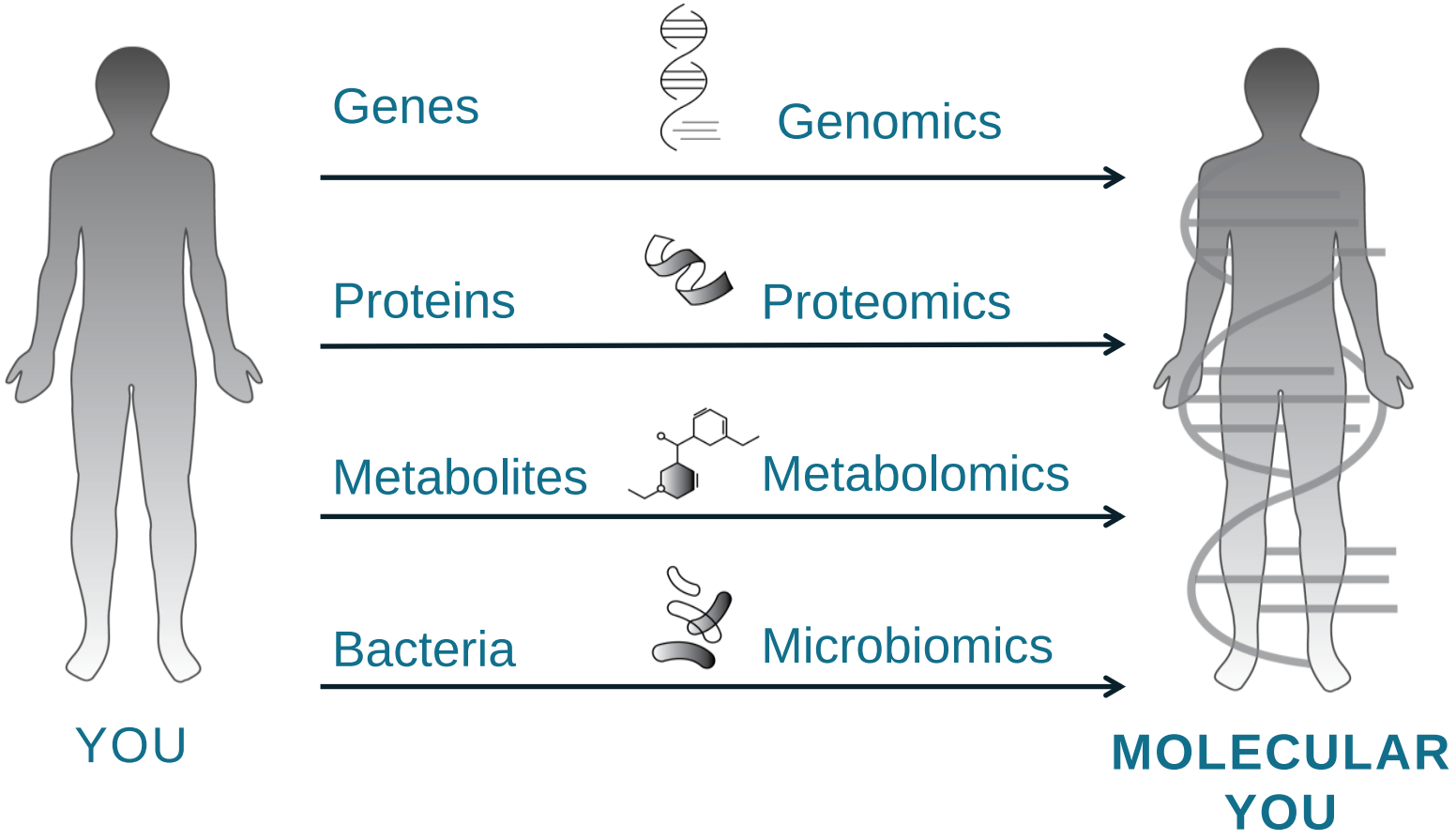
Clinical decision support systems (CDSS)

- Incorporate Omic profiling into clinical decision making
- The PMI has formed **GenXys Healthcare Systems** Inc. to construct CDSS for family practice physicians (match treatment to the patient and their disease)

molecular you PRECISION HEALTH

Molecular profiling to enable preventive medicine, achieve more precise diagnosis of disease and ensure better matching of therapy to disease

“Molecular You” Omic Profiling



MOLECULAR YOU PROFILING

molecular you

Genetic Profile

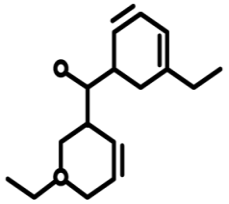
Analysis of genome sequence:
Exome

Protein Profile

Analysis of proteins in the blood:
192 proteins

Microbial Profile

Analysis of bacteria in gut :
>1,000 bacteria



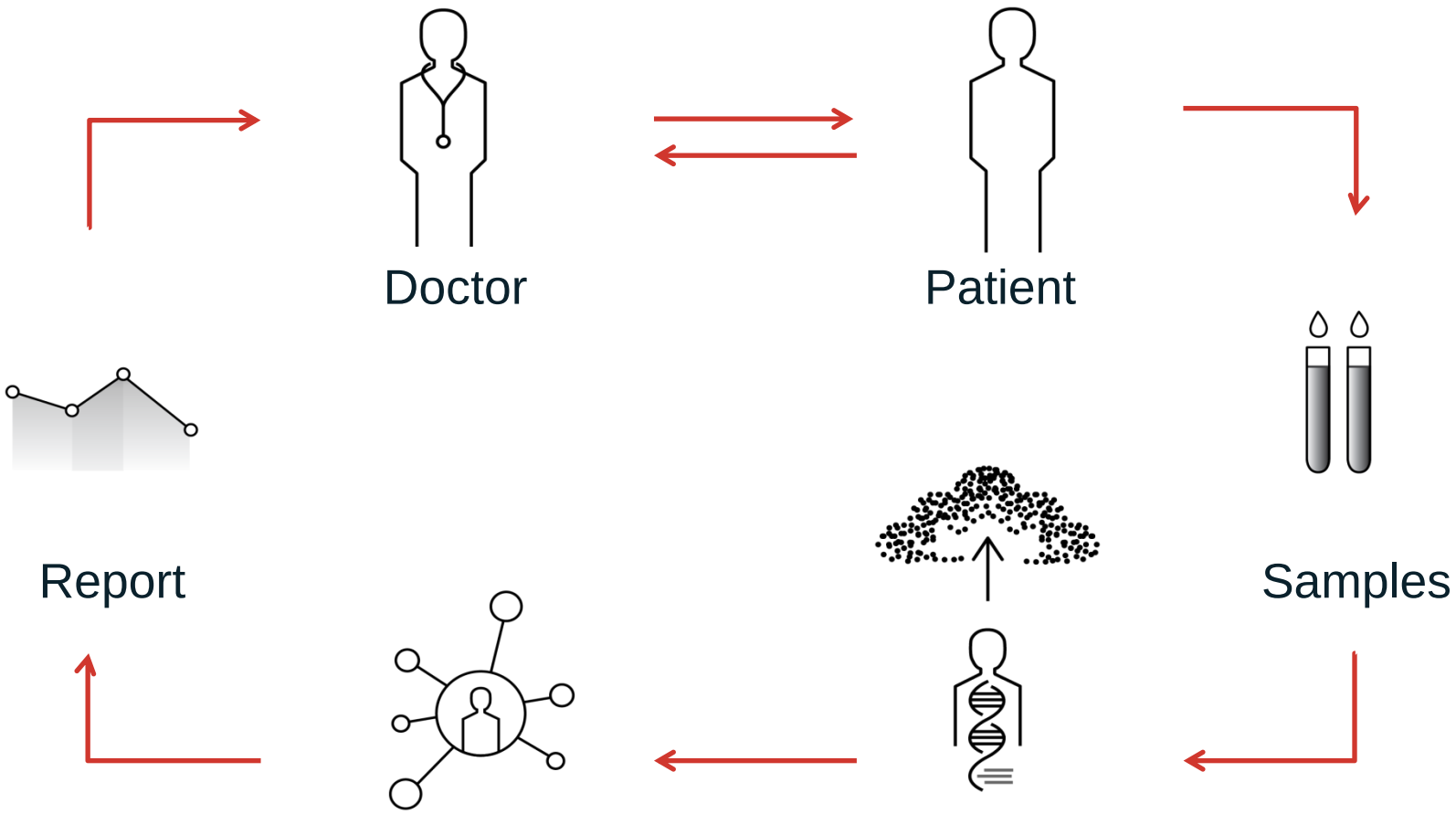
Metabolite Profile

Analysis of small molecules in urine and blood:
~300 metabolites

ONCE

FREQUENCY DETERMINED BY PARTICIPANT AND PRACTITIONER

The MYCO Process



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Your Data Cloud is Compared to an Up-to-Date Curated Reference Database

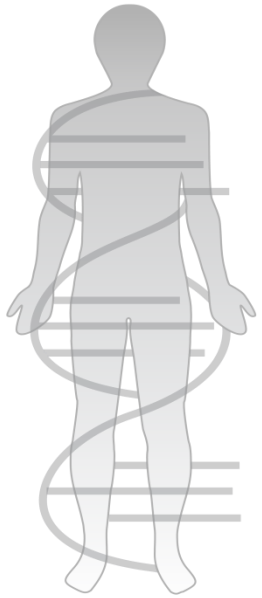
molecular you

Biomark DB

- Curated Metabolomic, Proteomic, Clinical Lab, Genomic and Microbiomic Data
  - Compared to scientific literature from human clinical trials: 1-12 studies per disease
  - Compared to established clinical reference values (Mayo Clinic, Ciba, Lab Tests On Line etc.)
  - Every measurement is compared to at least two reference values, average 5-6
- Reference database is kept up to date by full time curator
- Data entries must pass rigorous assessment

The MYCO Analysis Provides Diagnostics/Risk for 55 Diseases

- Heart disease
- Diabetes
- Hypertension
- Stroke
- Breast cancer
- Prostate cancer
- Colon cancer
- Lung cancer
- IBD
- Pancreatic cancer



MOLECULAR YOU

- Dementia
- Depression
- Autism
- Osteoporosis
- Arthritis
- Kidney disease
- Pneumonia
- COPD
- Multiple myeloma
- Leukemia
- etc

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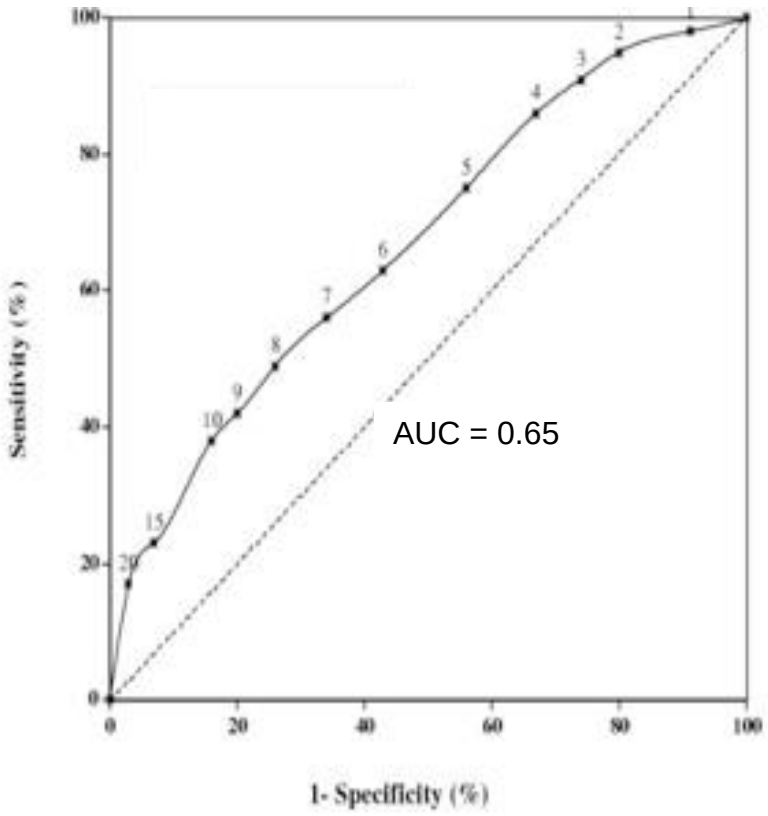
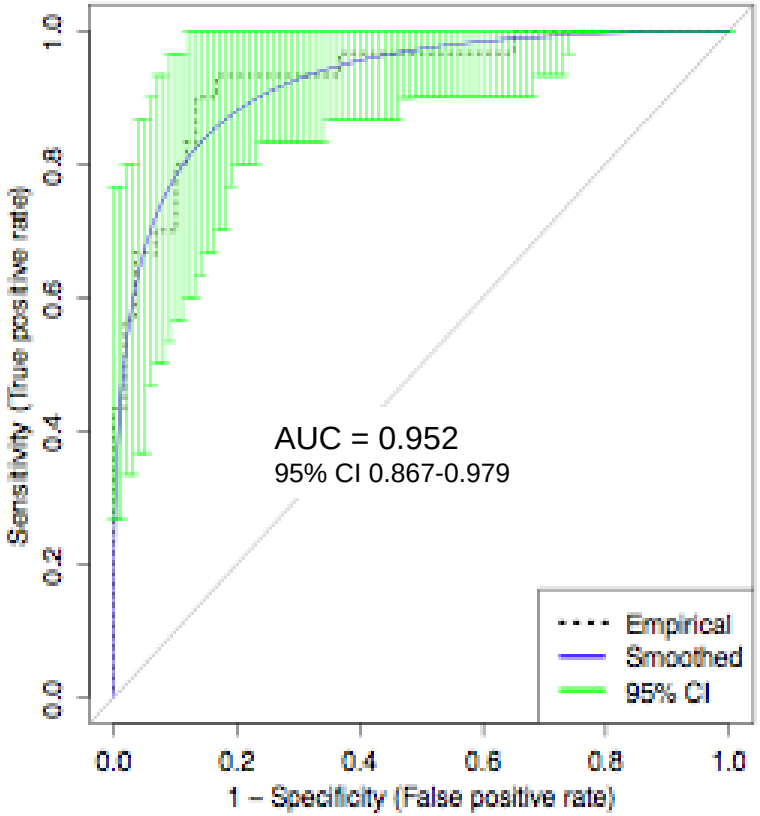
MYCO Diagnostics

Diagnostics covering ~55 diseases such as prostate cancer:

PSA



MYCO panel



PROOF OF CONCEPT— PATHFINDER STUDY

molecular you

Study parameters

- 11 healthy volunteers
- UBC, Vancouver General Hospital and St. Paul's Hospital Ethics Boards approval of the clinical study
- Phenotypic, genomic, proteomic, metabolomic and microbiomic data analyzed

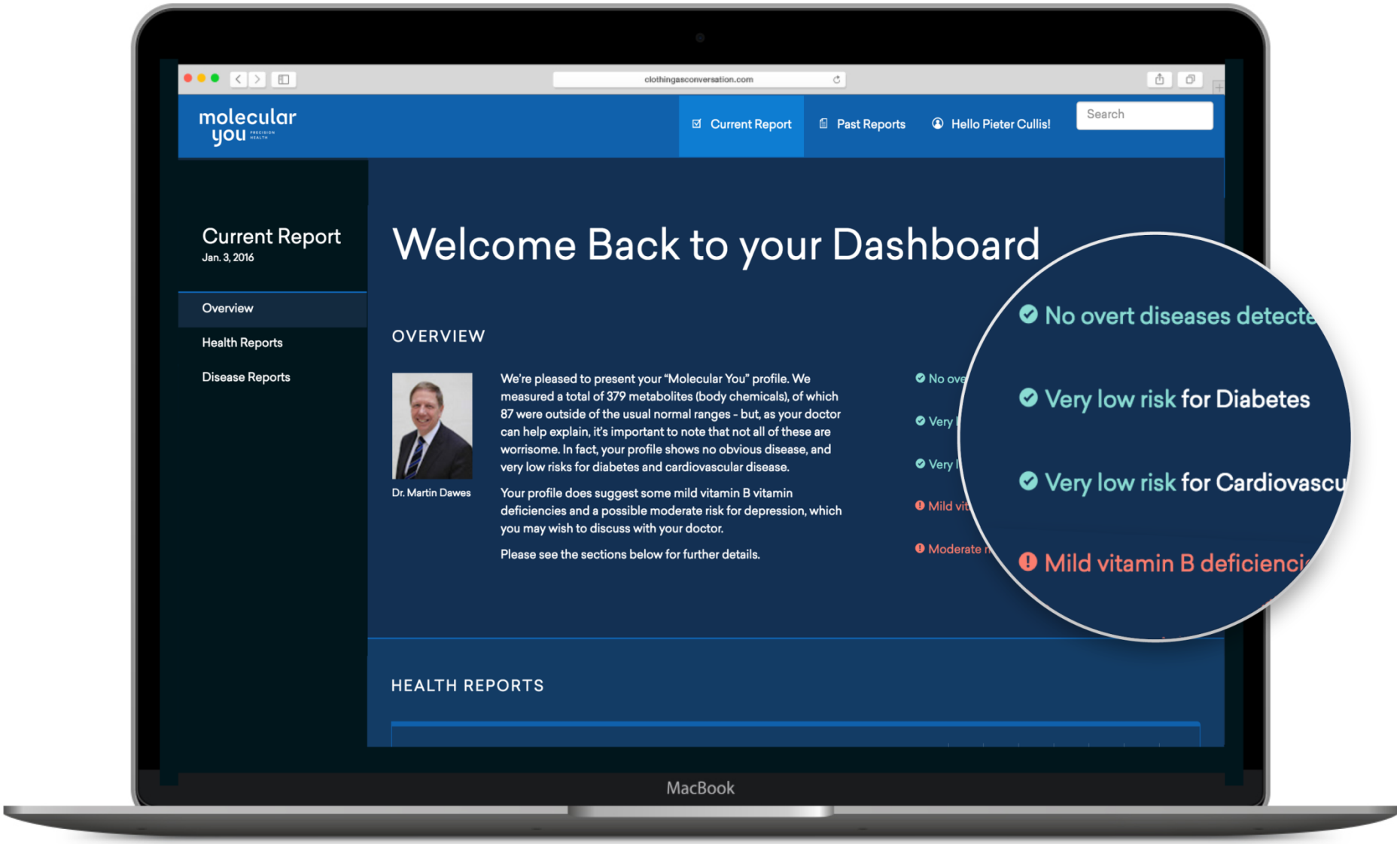
Results

- All participants had outliers in at least one measure with various degrees of severity
- One Pathfinder has agreed to share his data

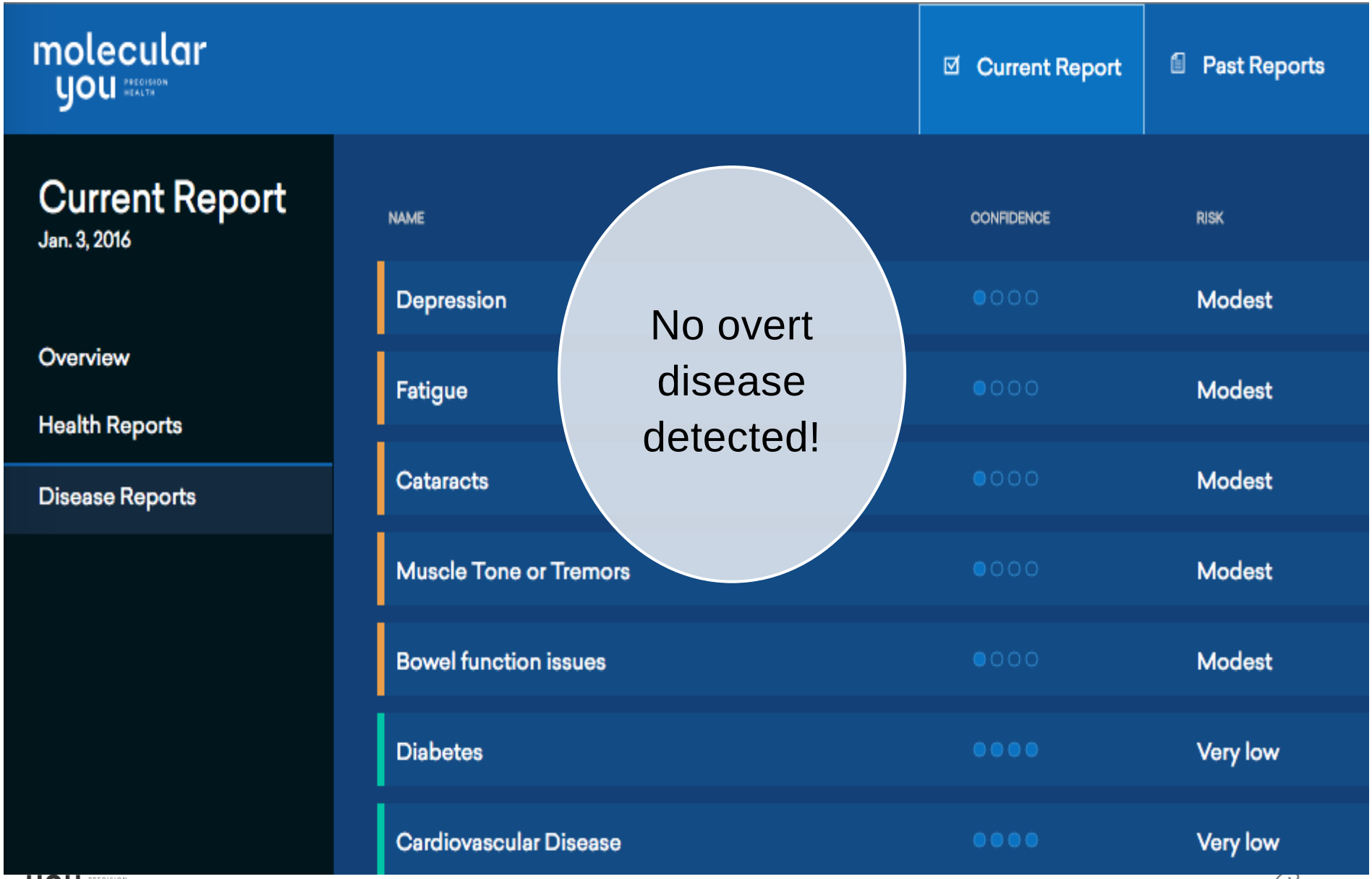
Interactive dashboard

- Level 1: Overview
  - a top line summary of your health
- Level 2: Disease risk report
- Level 3: Organ/system health summary
  - Brain, GI tract, heart, immune system, joint/muscle, kidney, liver metabolic etc
- Level 4: Details of organ/system health
  - Scientific literature

The MYCO Report: Overview



The MYCO Report: Disease Risk Report



The MYCO Report: Organ/System Health Reports

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Brain health is on the low side. Details are available by expanding this section

The MYCO Report: Brain Health

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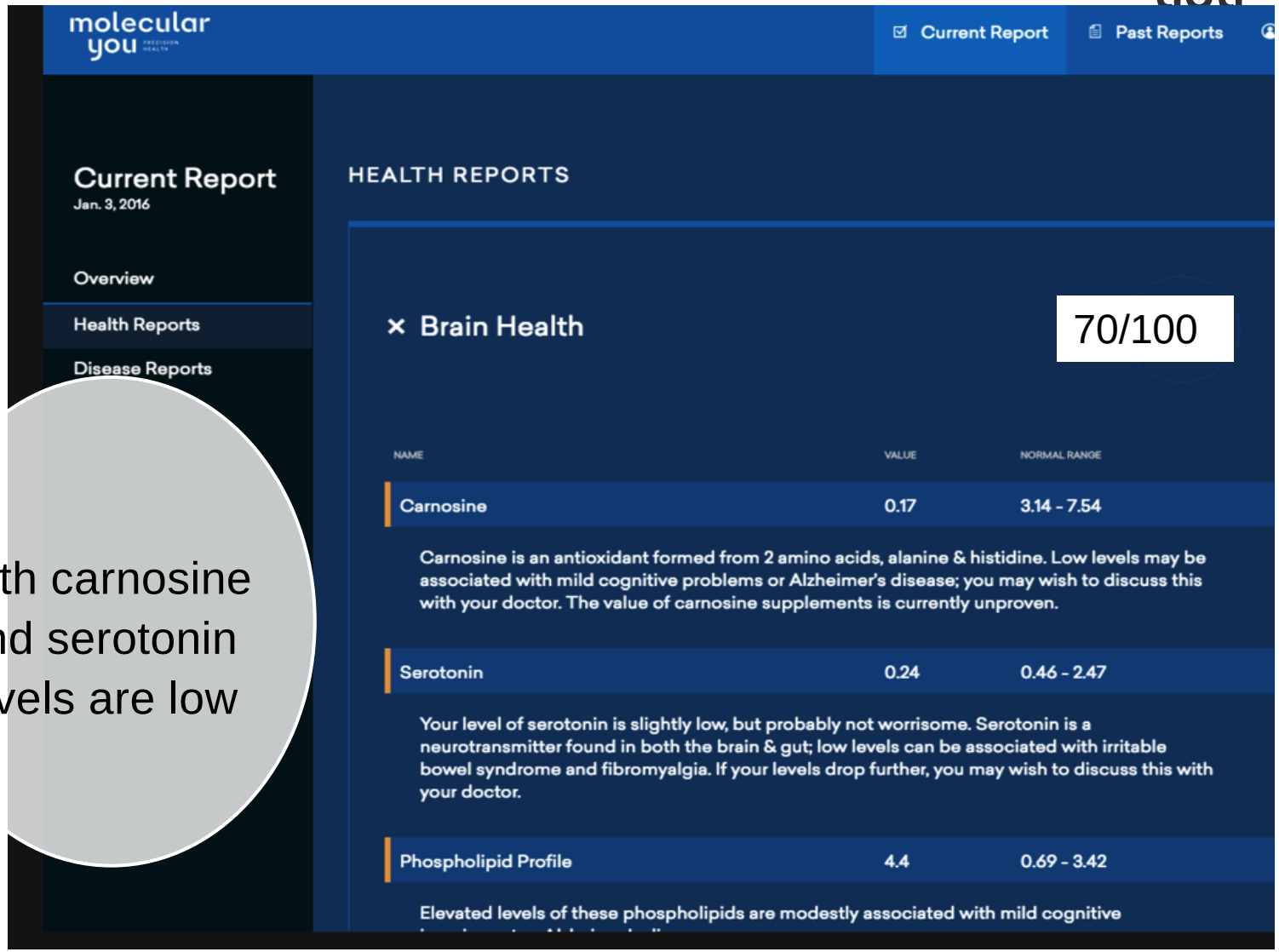

Both carnosine and serotonin levels are low

The MYCO Report: Nutritional Health

Vitamin B1 and B3 levels are low

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GenXys
Health Care Systems

Decision Support (*TreatG*$_x$)
to
Improve Medication Outcomes

Personalized Medicine Requires Clinical Decision Support Systems

Your doctor cannot incorporate individual molecular analyses into his/her decisions without a decision support system

Genetic guidance is contained in package insert for ~ 200 drugs, but never used in family practice

GenXys

Gout: Overview of Causes, Risk Factors & Incidence[2]

- **Uric acid crystals** may deposit in joints, nephrons & tissues (needle like, negative birefringent[3]). {↑serum uric acid (SUA) may contribute (>405μmol/L; theoretical saturation concentration)}
- **Pathophysiology**: ↑SUA: from ↓uric acid excretion [85%] or ↑ purine breakdown; most commonly secondary [70%] to drugs (chemotx, diuretics, ASA) disease (malignancies, renal dysfx, psoriasis), & dietary causes (beer, fish, red meat).
- **Risk factors**: ♂, CKD, HTN, obesity; hyperglycemia, hyperlipidemia, lead {Gout should prompt screen for conditions associated with CV risk!}[4,5,6]
  Precipitating factors: trauma, surgery, alcohol, starvation, ↑ purine foods & certain medications (see Drug Induced).
- **Incidence**: <1%; mostly elderly, ♂ & postmenopausal ♀[7,8]. Prevalence: ≤7% in ♂ >65; ≤3% in ♀ >85[3].

What are the stages and diagnostic criteria for gout?[3]

1) **Asymptomatic hyperuricemia**: ♂:>360-420μmol/L; ♀:>357μmol/L[7] (estrogen effect)
   - <25% go on to develop acute gout[7,9]. ↑ if SUA ≥500 μmol/L, >600μmol/L incidence ~6%[10].
   - *Usually* does not require drug treatment![9,10,25,31]
2) **Acute gouty arthritis**: quick onset 6-12hrs, *intense pain*, redness, heat & swelling, usually of one joint 90% of 1st attacks (commonly the big toe "podagra" 50%, ankle/foot, knee, finger, but also the olecranon, helix of the ear, &/or nephrons – uric acid tends to crystallize in the cooler parts of the body), pain peaks at 8-12hrs; often skin desquamation over affected joint / tendon. (May self-resolve in 3-7-14d [9,10]). SUA ↑or normal![7] **Elderly**: less pain; ↑ polyarticular, fever & delirium.
3) **Intercritical gout**: disease may progress despite symptom free period(s). {symptom free periods may decrease over time; initially may be years symptom free[10].}
4) **Chronic tophaceous gout**: tophi (progression to), bony erosions (deformations), nephropathy (stones)

What is the concern of diuretics with gout?

- Loop (e.g. furosemide) & thiazide diuretics ↓excretion & ↑concentration of uric acid.
- Hydrochlorothiazide induced gout: ~1%[11]; risk ↑ when dose ≥25mg/d[12]. Low dose thiazide (e.g. HCT12.5mg) often tolerated in patients with gout hx

What non-pharmacological therapies are recommended?

- **Acute attack**: rest, elevate limb, ice[13], avoid contact
- **Maintenance**: useful & may ↓ the need for preventative medications
  Diet: compliance with low purine diets is poor[14], recommend one less portion of meat or fish/day; drink wine instead of beer; drink a glass of *skimmed* milk each day.[15] Low fat dairy, fibre, ?Vit C, ?cherries & whole grains assoc. with ↓ gout.
  Low calorie diet more beneficial/acceptable than low purine diet!
  Avoid: liver, kidney, shellfish, gravy, sardine, sweetbread, Fructose[16], & yeast extract.
  Lifestyle: Weight loss!!! Smoking cessation! ↓ alcohol binging (especially beer)!
  ⇨ drink 2L water/day (unless CI'd), mild-moderate intensity exercise.

Are there any special treatment considerations?

- Lifelong tx may be required; however re-assess need for tx if attack free for many years &/or risk factors reversed; SUA levels may be useful[17].
- **Renal dysfx & very elderly**: adjust dose for allopurinol & colchicine; consider using colchicine or corticosteroids[18] as alternatives to NSAIDs.
- With NSAIDs, GI prophylaxis should be considered if history of PUD/GI bleed or ↑GI risk (age>70) {**PPI** omeprazole 20mg daily $32; or misoprostol 200mcg bid-qid $38-49}
- Review CV risk due to association of gout with CVD; CV protection with ASA 81mg po daily if 2° prevention; benefit supersedes the ↑risk of gout attacks.

What are the primary drug treatment options for gout? (ACR'12)

- **Acute attack**: *Rapid treatment initiation is key: <24-48hr.*
  {**Agent choice dependent on patient (severity, CI, DI, hx, SE, etc.)** [e.g. consider HF, renal fx, GI ulcer hx, diabetes, transplant hx, previous tx, age, DIs.]}
  - **Colchicine** (eg. 0.6mg BID x1-3 days, then daily); stop after ≥1-2wk (start within 36hrs) {**FDA July/09**: 1.2mg po immediately, then 0.6mg once in 1hr (RCT)}
  - **NSAIDs** – Full/high doses to achieve pain relief until 48hrs after symptom resolution (or ~3 days); then stop or taper over 1-2 weeks
  - **Corticosteroid** IM methylprednisolone, PO prednisone (or Intra-Articular Betaject, Aristospan)[18,19,20] {May add acetaminophen to corticosteroid if NSAIDs & colchicine CI'd[21]}

  NOTE: Do not start, stop or adjust **allopurinol** during an acute attack!
- **Maintenance/Prophylaxis**[22]: Motivation to take meds may wane over time if no symptoms.
  - **1st attack**: lifestyle changes & remove drug causes if possible
    Treat if: 1) recurrent attacks (≥2/yr); 2) ↑SUA levels (>800μmol/L); 3) chemotx; 4) advanced dx tophus/tophi or urolithiasis; 5) CKD ≥Stage 2
  - **1st Line: allopurinol**[23] (Start low, go slow, & prophylax as below!)
    - **Consider waiting 1-2wks after inflammation settles before initiating allopurinol** (fluctuating SUA, prolong attacks, may destabilize crystals)
    - **Prophylax with colchicine** low dose **or an NSAID** not ASA[24] **while titrating/adjust allopurinol** (usually ~ 3 – 6+ months[17]) **unless CI'd**
    - **Target SUA levels: <300 to 360μmol/L**[1,7,17]. Lifelong treatment.
  - **Alternative: colchicine** (low dose ≤ 0.6mg daily); may not prevent complications {Alternative: probenecid rarely an option (SAP access), but requires renal fx ≥50ml/min} (ACR'12)

Generic/TRADE (Strength & forms) g=generic	Class / Pregnancy category[25]	Side effects / CI: Contraindications	√ = therapeutic use / Comments / Drug Interactions DI / Monitor M	Dosing: {for acute tx with NSAID or colchicine, Initial x 1-3 days ⇨ Follow-up x1-2+ wks}	$/30d
Naproxen NAPROSYN,g ALEVE (OTC) 125,250,375ς,500ς,750mg SR tab 500mg supp, 25mg/ml susp (OTC)	NSAIDS (non-ASA) -↓pain & inflammation [P1 P3 L] For more info on NSAIDs, Acet, & Coxibs, see RxFiles PAIN charts at www.rxfiles.ca	Common: n/v (Indomethacin: GI upset, headache, ↑SE especially CNS, & in elderly) CI: ↓ Renal (Stage ≥IV CKD), GI ulcer, HF, transplant Precautions: CVD; (Avoid Indocid ≥65yrs) {Indomethacin used historically; however others effective & less CNS SE's!}	√ Gout – for acute attack or when initiating allopurinol GI prophylaxis (if indicated) with a PPI or misoprostol[17] DI: Li^{++}; ACEI/ARBs (minor DI, except ↑K^+ if on NSAID, spironolactone & ACEI or ARB) M: follow-up 4-6wks after acute attack to assess need of further tx; if at renal risk Na^+ @24hr, SCr @72hr {Can use in CKD stage 1-2 & dialysis; avoid in stage 3 if CrCl ≤40ml/min & CKD stage 4.} Acute: High doses for 1st 24-72hrs of attack. Then stop, or use lowest effective dose over 1-2wks.	500-750mg x1; 500mg BID; ⇨ 250-500mg BID Max ≤ 1500mg/d x1day/short term. ⇨ Usual Max 1000mg/d	16-20
Ibuprofen MOTRIN, ADVIL,g 300,600mg tab; (200,400mg) (OTC)				600-800mg po TID; ⇨ 400-600mg TID Max 2400-3200mg	12-21
Indomethacin INDOCID,g 25,50mg cap; 50,100mg supp				25-50mg po TID; ⇨ 25mg BID-TID Max 200mg/d {Historically used but other NSAIDs now preferred.}	14-23
Celecoxib CELEBREX 100,200mg cap	COX-2 specific inhibitor [P L] -↓ pain & inflammation	Common: GI maybe less than some other NSAIDS CI: CVD, Renal dysfx Precautions: GI ulcer	√ Gout–acute attack or when initiating allopurinol DI: Li^{++}, ACEI/ARBs M: follow-up 4-6weeks after acute attack to assess need of further tx	100-200mg po BID; ⇨ 100-200mg OD-BID Max 400-800mg/d	54
Acetaminophen TYLENOL,g 325,500,650mg tab ▼ OTC	Analgesic [P L] -↓ pain (minimally effective)	Common: rash Serious: hepatotoxicity Precautions: Liver dysfx &/or alcoholism	√ Mild gout associated pain &/or in combination with corticosteroids. DI: Warfarin if ↑ dose acetaminophen M: Liver function tests if long term & ↑EtOH intake	650-1000mg po q6h (prn; adjunct to CS) Max 4000mg/d	15-25
Colchicine COLCHICINE-ODAN,g 0.6ς,1ς mg tab [Colcrys USA] IV Colchicine not recommended →toxicity[10] [P L]	Anti-gout: ↓ pain, inflammation: ↓'s urate crystal deposition by: ↓leukocyte motility, phagocytosis, etc. Familial Mediterranean Fever 1.2-2.4mg/d; 1° prevention: Postpericardiotomy Sx	Common: NVD 80% @high dose; 4-25% @low dose → ↓dose/stop; rash, alopecia. Serious: neutropenia, myopathy, liver, rhabdomyolysis. Precautions: CVD; ↓ renal fx ↓dose CI: blood dyscrasias, solid organ transplant; ? maybe dialysis	√ Gout –acute attack or if initiating allopurinol[24]; {SE with high doses however limiting to ≤3 tabs on 1st day then 1-2 tabs/day will ↓↓↓ diarrhea/GI side effects!!!} DI: cyclosporine ↑myopathy, P-gp & 3A4 inhibitors: clarithro & erythro-mycin, ketoconazole, verapamil, diltiazem, juice M: CBC neutropenia, Creatine Kinase rhabdomyolysis: may ↑ with statin/fibrate & renal fx q6mon	Initial: 1.2mg x1 stat, then 0.6mg in 1hr or 0.6mg po BID-TID x1-3 day ⇨ then OD x 7-10+ day. 0.6mg OD or bid for ~ 3 - 6+ months if starting allopurinol {If ↓renal fx, ↓dose to every other day if prolonged tx 10+ days}	12-17 16 - 26
Methylprednisolone acetate DEPO-MEDROL,g 20X▼,40,80mg vial [P L] **Triamcinolone** acetonide KENALOG 10 & 40,g 10mg/ml 5ml, 40mg/ml 1ml, 40mg/ml X▼ 5ml vial [P L]	Corticosteroids/ -↓ inflammatory response Hydrocortisone SOLU-CORTEF 100,200mg vial	Common: inj site rx Serious: edema/HF; SE: Caution in long term, but rare in short term Precautions: systemic & viral infections, immunosuppression, local skin atrophy Glucocorticoid: Prednisone 5mg = Methylprednisolone 4mg	Useful if CI/SE's to NSAIDs & colchicine eg. for renal, transplant, warfarin pts, etc. √IM or IA inj x1: monoarticular attack √IM or oral: polyarticular attack DI: aprepitant ↑CS levels, vaccines DI: rare with intra-articular minimal systemic absorption M: osteoporosis risk if prolonged / frequent use; diabetes: ?? ↑BG testing (IA: suggest minimum 3 months between treatments) {Betamethasone (sodium phosphate & acetate; Fast acting & Long acting) BETAJECT 3mg/1ml vial ⊗ MJA $9/vial} {Triamcinolone hexacetonide ARISTOSPAN 20mg/1ml vial ⊗ pedx; ▼; $7/vial}	IM: Methylprednisolone: 40-80mg IM x1 Pending age / degree of inflam IA: Small joints Phalanges: Methylpred 4-10mg IA; 8mg Triamcin 2.5-5mg IA; 10mg Betameth 1.5-3mg IA; 3mg IA: Large joints Knees/ankles: Methylpred 20-80mg IA; 40mg Triamcin 5-15mg IA; 40mg Betameth 1.5-3mg IA; 6mg	5-9/vial 9/1ml vial 5/1ml vial
Prednisone WINPRED,g 1,5ς,50ς mg tab (Prednisolone 1mg/ml susp) [P L]	Methylprednisolone MEDROL 4ς,16ς mg tab	Common: insomnia, ↑BP, ↑BG, GI upset, mood △ Serious: most rare in short term; edema/HF		25-50mg po daily x 3-5 days & stop[20]; no taper! {If catch early e.g. 1st sign, 10mg x1-2 may be adequate}	15
Prophylaxis: **Allopurinol** ZYLOPRIM,g 100ς,200ς,300ς mg tab [P L]	Xanthine oxidase (Xanthase) inhibitor -↓uric acid production -↓BP in young hypertensive pts -Adjunctive to K+ citrate for uric acid stones	Common: rash[2%], diarrhea Serious: Allopurinol hypersensitivity syndrome <1% (≤30% mortality! ↑risk if ↓ renal fx (eg. ACEI, NSAID), elderly, diuretic use): start low! Stevens-Johnson Sx[26] ↑with HLA-B*5801-Asian CI: Acute gout Precautions: renal ↓dose or liver dysfx	√ Maintenance; adjust dose for SUA, renal fx, tolerability & response DI: rash maculopapular when used with ampicillin ~20%/amoxicillin; antacids, thiazide, ACEI; ↑ toxicity of 6-MP, azathioprine, cyclophosphamide & theophylline ↑; warfarin ↑INR M: SUA & renal fx q3mon 1st year then q6mon[10] (See CPS for dosing info in ↓renal fx) Note: Allopurinol desensitization[27] possible (susp ↑'s from ≤50ug to 100mg over ≥28day).	Start at 100mg; ↑100mg q2-4wks ↓risk of rash, etc. Usual dose: 300mg daily, preferably after food Usual range: 100-800mg (divide doses ≥300mg to ↓GI SE) If CKD, hepatic impairment, or elderly start 50mg/day; ↑ 50mg increments. MAX 300mg/d	15 10-26
Prophylaxis: **Febuxostat** ULORIC[28], New Canada, ☎ ⊘ 80 mg tab	Xanthine oxidase inhibitor like allopurinol but unique structure [P L]	Common: ↑LFT 5-7%, nausea, arthralgia, rash Serious: ?MI, ?stroke	DI: azathioprine, didanosine, mercaptopurine, theophylline (↑levels of each) M: LFT (@2-4 mo, then periodically) Note: may ↓uric acid > allopurinol, but no less attacks	40-80mg tab po daily (lack of data for use in CrCl <30ml/min) More flares during initiation than allopurinol. Max 120mg/day	55

= ↓ dose for renal dysfunction ς=scored tab X=Non-formulary Sask ⌢=Exception Drug Status Sask. ⊗=not covered by NIHB ▼=covered by NIHB ⊘=NIHB EDS **ACEI**=ACE inhibitor **BG**=blood glucose **BP**=blood pressure **CI**=contraindication **CKD**=chronic kidney disease **CS**=corticosteroids **CVD**=cerebral vascular disease **DI**=drug interaction **dx**=diagnosis **fx**=function **GI**=stomach **HF**=heart failure **HR**=heart rate **HTN**=hypertension **hx**=history **IA**=intra-articular **Li**=lithium **M**=monitor **MI**=myocardial infarction **n/v**=nausea/vomiting **OTC**=over the counter **pt**=patient **SE**=side effect **SUA**=serum uric acid **sx**=symptoms **tx**=treatment **wt**=weight

Uricosurics: (rarely used): Probenecid BENURYL,g D/C; SAP 500ς mg tab; 1g BID $34 (0.5-2g/d); SE: rash, GI upset; CI: nephrolithiasis Hx; renal: ineffective if CrCl<50mL/min; Drink 2L H_2O/d. DI: ASA, azathioprine, MTX. {Also Sulfinpyrazone ANTURAN g, 200mg tab; 100-200mg BID $17-27; no longer used.}

Other Meds for Tx: Oxypurinol[29] oral allopurinol metabolite in trial; losartan & fenofibrate[30]: modest uricosuric effect (potential losartan or calcium channel blockers if gout + htn); Opioids possible adjunct analgesic[31]; ACTH 25-40 IU SC[10]; Anakinra: 100mg SC daily x3days. **Goals**: ↓acute inflammation, prevent flares, ↓SUA

Pegloticase: USA: Krystexxa urate oxidase enzyme, 8mg IV over ≥2hr q2-4wk, allergic rx, CI: G6PD, ↑↑ SUA. Benzbromarone ↑urate excretion; orally special access CDN[32] & Ketorolac IA inj; Rasburicase IV: USA for tumor lysis sx in cancer pt. CI: G6PD HERBAL: no documented efficacy; ?(caffeine[33], devil's claw & garlic). Anecdotal support: berry juice/ berries

Rule out: Pseudogout[34] (calcium pyrophosphate CPPD crystals in synovial fluid, commonly the knee), "Appears like OA, but in all the wrong places" possibly tx with colchicine 0.6mg/d or CS; Septic arthritis aspirate joint, WBC, temperature & vitals, do gram stain & culture; & Rheumatoid arthritis.

Drug induced: acetazolamide, ASA low dose, chemo, cyclosporine, diuretic, ethambutol, lead, levodopa, niacin, tacrolimus, teriparatide, ?ticagrelor **Food induced**: purine rich eg. red meat, fish, beer, spirits **Diagnosis**: Diagnostic certainty→ analyze synovial fluid for uric acid crystal or id'ing tophus containing uric acid crystal under polarized light microscopy. May see "mouse bite" erosions. Optional 24hr urine collection: to see if ↓excretor or ↑producer[3,10] but does not alter tx; (if uric acid excretion ≥1g with reg. diet→over-producer, if CL uric acid <6mL/min→under-excretor) since allopurinol effective for both[1].

Diagnostic Rule Variables: male sex, previous patient-reported arthritis attack, onset within 1 day, joint redness, first metatarsophalangeal joint (MTP1) involvement, hypertension or ≥1 cardiovascular disease, & serum uric acid level >350umol/L. www.umcn.nl/goutcalc Janssens'10

GenXys Addresses Basic Problems With Drug Prescription

Adverse Drug Events	Ineffective Drugs	Genetic Variations	Medication Selection
4th leading cause of death	60% of prescribed drugs do NOT benefit the individual	97% of the population has at least 1 actionable genotype	Genetics is only 1 element of the complex drug selection process

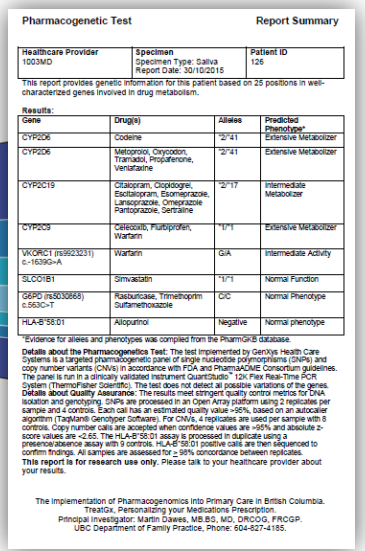
GenXys

Genetic Analysis

Saliva based PCR technology genetic test for variants that affect the level of activity of medications used in primary care.

Analyzing 33 SNP's - moving to 120 SNP's.

Analysis includes variants in CYP2D6, CYP2C19, CYP2C9, VKORC1, HLA-B*58:01, G6PD and SLCO1B1.



Pharmacogenetic Test **Report Summary**

Healthcare Provider	Specimen	Patient ID
1003MD	Specimen Type: Saliva Report Date: 30/10/2015	126

This report provides genetic information for this patient based on 25 positions in well-characterized genes involved in drug metabolism.

Results:

Gene	Drug(s)	Alleles	Predicted Phenotype*
CYP2D6	Codeine	*2/*41	Extensive Metabolizer
CYP2D6	Metoprolol, Oxycodon, Tramadol, Propafenone, Venlafaxine	*2/*41	Extensive Metabolizer
CYP2C19	Citalopram, Clopidogrel, Escitalopram, Esomeprazole, Lansoprazole, Omeprazole Pantoprazole, Sertraline	*2/*17	Intermediate Metabolizer
CYP2C9	Celecoxib, Flurbiprofen, Warfarin	*1/*1	Extensive Metabolizer
VKORC1 (rs9923231) c.-1639G>A	Warfarin	G/A	Intermediate Activity
SLCO1B1	Simvastatin	*1/*1	Normal Function
G6PD (rs5030868) c.563C>T	Rasburicase, Trimethoprim Sulfamethoxazole	C/C	Normal Phenotype
HLA-B*58:01	Allopurinol	Negative	Normal phenotype

*Evidence for alleles and phenotypes was compiled from the PharmGKB database.

Details about the Pharmacogenetics Test: The test implemented by GenXys Health Care Systems is a targeted pharmacogenetic panel of single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) in accordance with FDA and PharmaADME Consortium guidelines. The panel is run in a clinically validated instrument QuantStudio™ 12K Flex Real-Time PCR System (ThermoFisher Scientific). The test does not detect all possible variations of the genes. **Details about Quality Assurance:** The results meet stringent quality control metrics for DNA isolation and genotyping. SNPs are processed in an Open Array platform using 2 replicates per sample and 4 controls. Each call has an estimated quality value >95%, based on an autocaller algorithm (TaqMan® Genotyper Software). For CNVs, 4 replicates are used per sample with 8 controls. Copy number calls are accepted when confidence values are >95% and absolute z-score values are >2.65. The HLA-B*58:01 assay is processed in duplicate using a presence/absence assay with 9 controls. HLA-B*58:01 positive calls are then sequenced to confirm findings. All samples are assessed for ≥ 98% concordance between replicates. **This report is for research use only.** Please talk to your healthcare provider about your results.

The Implementation of Pharmacogenomics into Primary Care in British Columbia.
TreatDx, Personalizing your Medications Prescription.
Principal Investigator: Martin Dawes, MB.BS, MD, DRCOG, FRCGP.
UBC Department of Family Practice, Phone: 604-827-4185.

Algorithm Formation

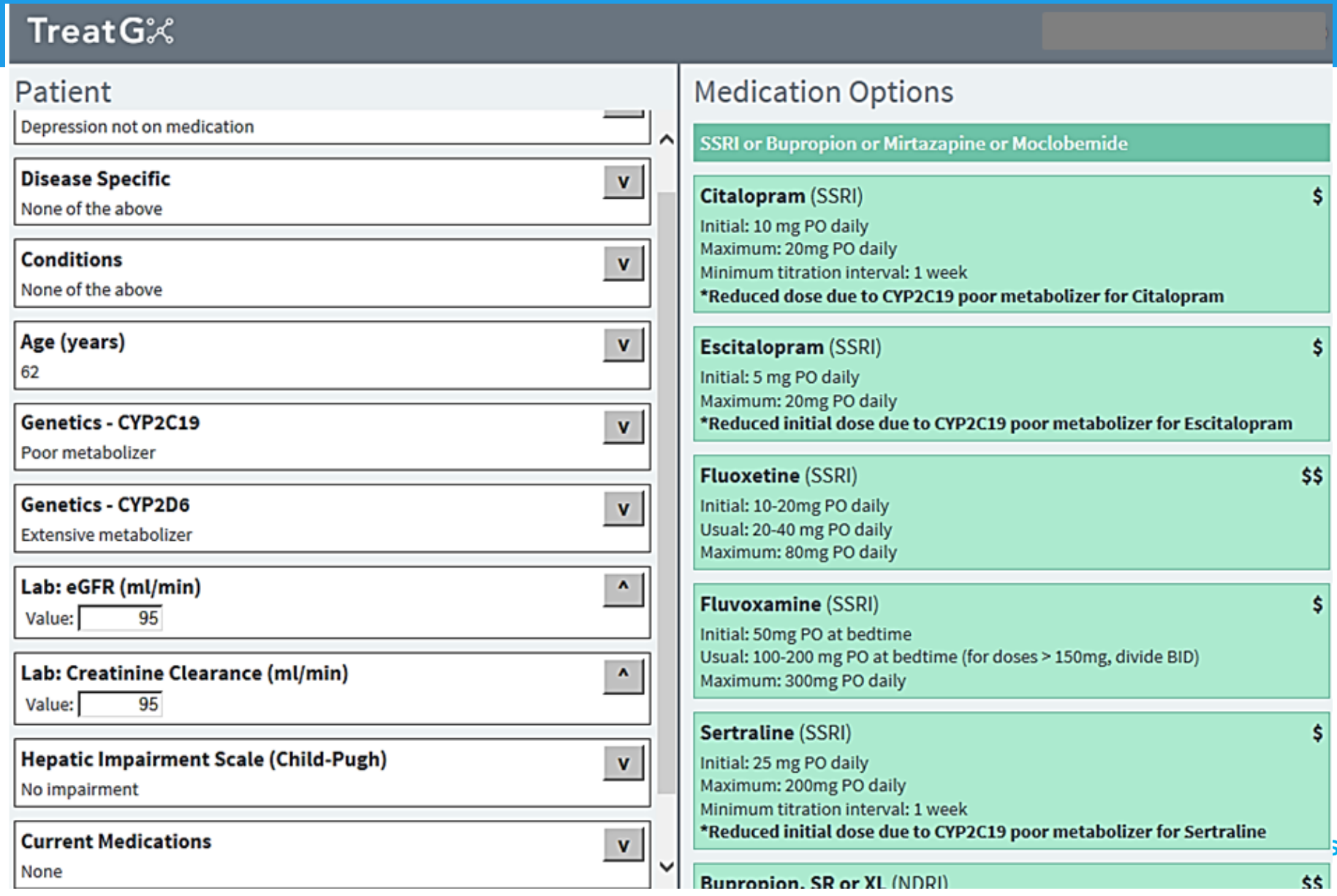
Algorithms written using the highest levels of evidence using:

- Patient characteristics; age, gender etc
- Co-morbidities
- Drug-drug interactions
- Drug side effects
- Pharmacogenetic interactions
- Drug costs

TreatGx Process

- Multiple SNP panel analysis previously entered into patient's EMR
- Physician makes diagnosis, enters diagnosis into EMR
- Algorithm provides a list of drugs that are safe for that patient to take
- Physician can query to find reasons for recommendations if desired

TreatGx Decision Support



GenXys Has Considerable Potential to Reduce Healthcare Costs

Population of Canada	→	35,800,000
Canadians over 45 with chronic disease	→	10,507,225
Canadians over 65	→	5,400,000
Canadians over 65 taking 10 or more drugs	→	1,080,000

Implementation of GenXys would save Canada
>$1 Billion per year in hospitalizations and ER Visits

Dionne and Mitton

ER visits would decline 71%, Hospitalizations by 39%

Journal of Medical Economics (2015)

GenXys

The PMI is Attempting to Provide "End-to-End" Solutions for Introducing Personalized Medicine Into the Population

Preventive Medicine

- Molecular You profiling over time to determine trends, effectiveness of lifestyle/therapy

Accurate Diagnostics

- Molecular You profiling to detect disease

Appropriate Therapy

- GenXys CDSS to guide drug prescription in family practice

Acknowledgements

Martin Dawes, Head Family Practice, UBC; CMO GenXys

David Wishart, Director Metabolomics Centre, U Alberta; CIO Molecular You

Rob Fraser, CEO Molecular You Corporation

Bruce McManus, Director Prevention of Organ Failure, St. Paul's Hospital

David Huntsman, Director Centre for Applied Genomics, BC Cancer Agency

James Russell, ex-Head Medicine, St. Paul's Hospital