Clinical Genomics in a Children's Hospital

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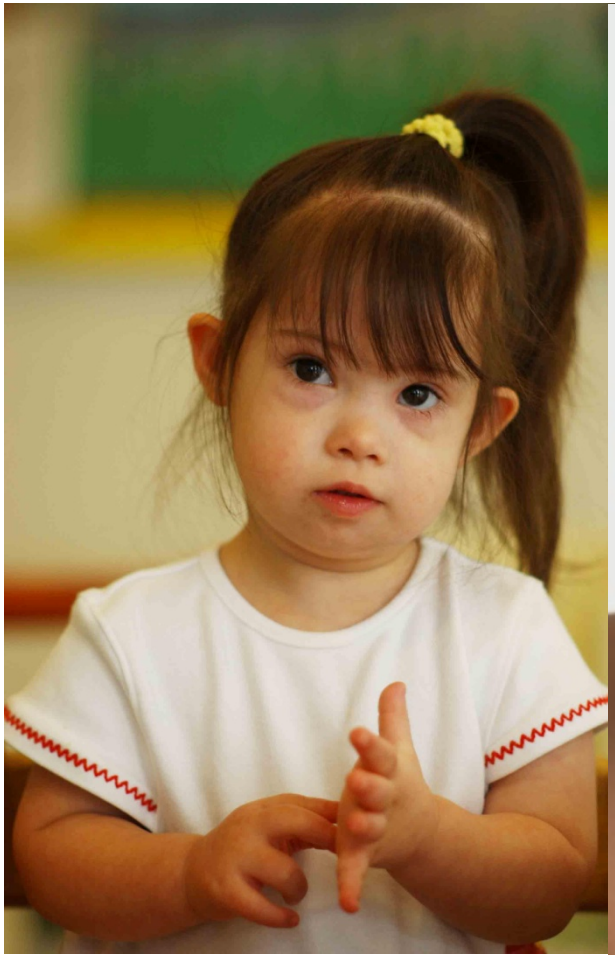
Cincinnati Children's Hospital Medical Center
Cincinnati

Genomic Medicine 4
Dallas
Tuesday, January 29, 2013

Cincinnati Children's Hospital Medical Center



Cincinnati &
Cincinnati Children's Hospital

Cincinnati Children's Hospital Medical Center

- 1,144,858/y Patient Visits
- 70,000/New Patients
- 5,000/y NICU Admissions
- 6,365/y I/P Surgeries
- 27,000/y O/P Surgeries
- 550 Liver Transplants Procedures (>400 survivors)
- 3,500/y Adenoidectomies
- 3,000 Peña Procedures
- 250 Nuss Procedures (76 in 2012)
- 822 Faculty
- 13 Off-site Outpatient Clinics
- 512 Inpatient Beds
- 13,000 Employees
- $1.4 Billion Gross Income
- $173 Million Research Funding (13% Increase over 2011) ($107 Million from the NIH)
- Epic Electronic Record
- Cerner Lab Record
- 24 heart transplants with 100% survival (2011 & 2012)

Genomic Medicine at CCHMC

- Existing
  - Individual gene sequence
  - Infectious disease Dx
  - Cytogenetics
  - Pharmacogenomics
- Underway
  - Targeted gene sequencing
  - Whole exome sequencing
- Probable Future…
  - Gene expression -- Methylation
  - DNAse sensitivity -- Histone marks
  - Genome sequence -- ChIP sequence

2012 Genomic Medicine Financing

CCHMC Human Genetics

- Bill: $11 million
- Collect: $7 million

CCHMC Cytogenetics

- Bill: ~$4 million
- Collect: ~$2.4 million

Other Service Providers

- Cost: $2 million
  - Athena Diagnostics
  - Prometheus
  - Gene DX
  - Baylor Genetics
  - Ambry Genetics
  - Others

Genetic Pharmacology Service, Psychiatry Panel

Genetic Pharmacology Service

Adult and Pediatric Psychiatry Panels Available

The Genetic Pharmacology Service for children and adults at Cincinnati Children's Hospital Medical Center offers drug panels for many commonly prescribed psychiatry medications.

The table below lists the panels currently available through the Genetic Pharmacology Service at Cincinnati Children's.

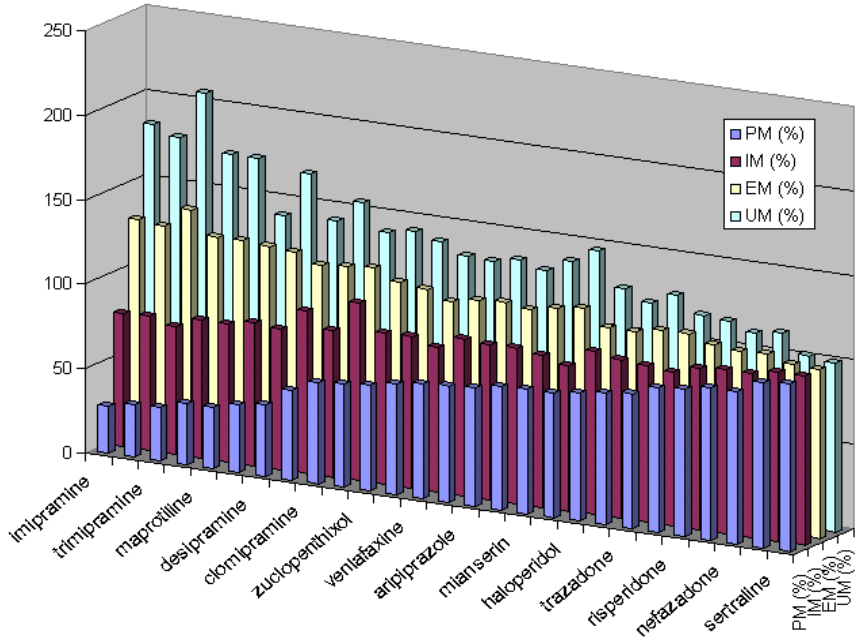
View List of Drugs Tested

Psychiatry Panel

Amitryptiline	Fluoxetine	Moclobemide	Sertraline
Aripiprazole	Flupentixol	Nefazadone	Thioridazine
Atomoxetine	Fluvoxamine	Nortriptyline	Trazadone
Buproprion	Haloperidol	Olanzapine	Trimipramine
Citalopram	Imipramine	Paroxetine	Venlafaxine
Clomipramine	Levomepromazine	Perazine	Zotepine
Clozapine	Maprotiline	Perphenazine	Zuclopenthixol
Desipramine	Mianserin	Pimozide	
Doxepin	Mirtazapine	Risperidone	

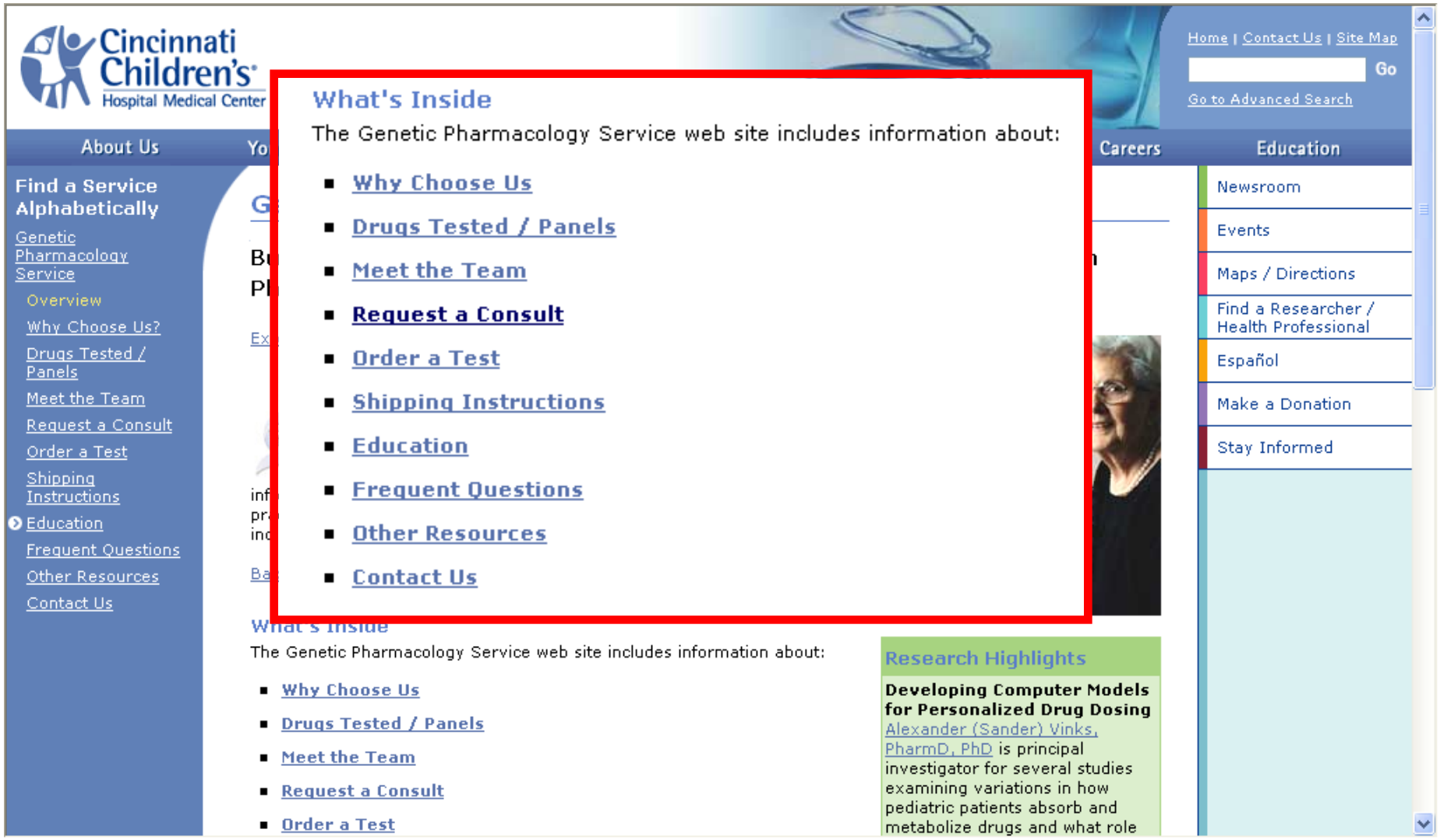
Included in the patient report

- Test performed
- Genotype (allelic information)
- Predicted phenotype (e.g. Poor Metabolizer, etc.)
- Dosing recommendation(s)
- List of drugs that cause serious drug-drug interaction
- Test limitations
- Location of supplemental information
- How to order a GPS consult

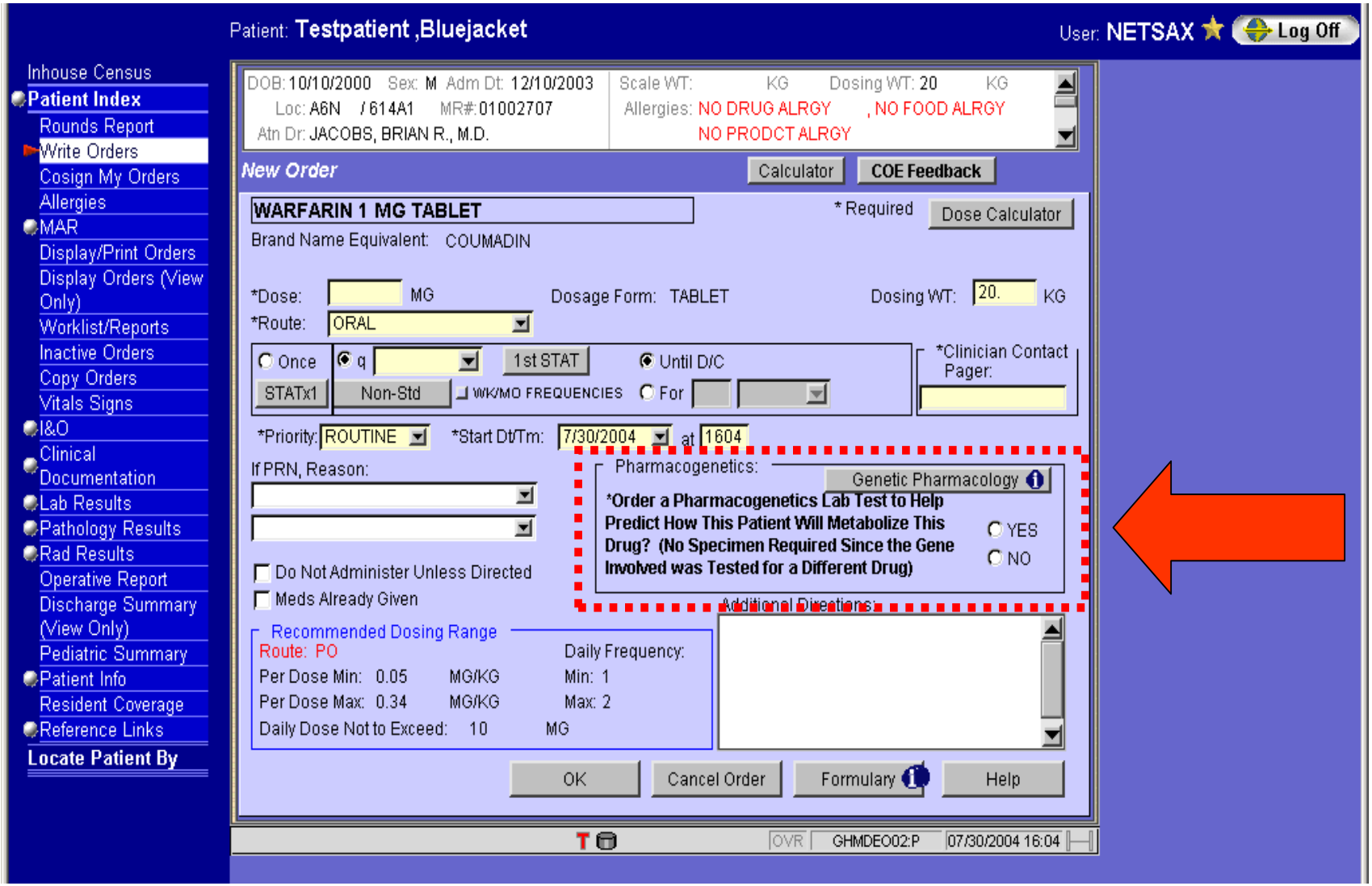


Kirchheiner J, et al. Molecular Psychiatry Feature Review 2004
Meta-analysis of published research from 1970-2003 on the relevance of PG effects of CYP2D6 and CYP2C19 on 36 antidepressants and 38 antipsychotics

Genetic Pharmacology Service
http://gps.cchmc.org



PG linked to inpatient medication ordering



Genetic Pharmacology Service

- Order by drug name – not by specific gene
- Rapid turn around time: 2 business days
- Report includes
  - Dosing recommendations based on genotype
  - Identification of other drugs that induce, inhibit or interact with drug in question
- Provide consultative service if needed
- Provide educational materials for health care professionals, families and patients

Experience to Date – Lessons learned

- Used in > 8,000 pediatric patients
- Most commonly used for:
  - inpatient and outpatient pediatric psychiatry patients
  - children with autism
- Marked differences between physicians regarding knowledge about impact of genetic variation on drug metabolism
  - Some want gene name
  - Some drug name
  - Some want panel to cover potential drugs

Methods: Weight-Free Behavioral Intervention Score (BIS)

- Behavioral interventions: x_1: seclusions or timeouts [summed], x_2 : holds, and x_3 : restraints.

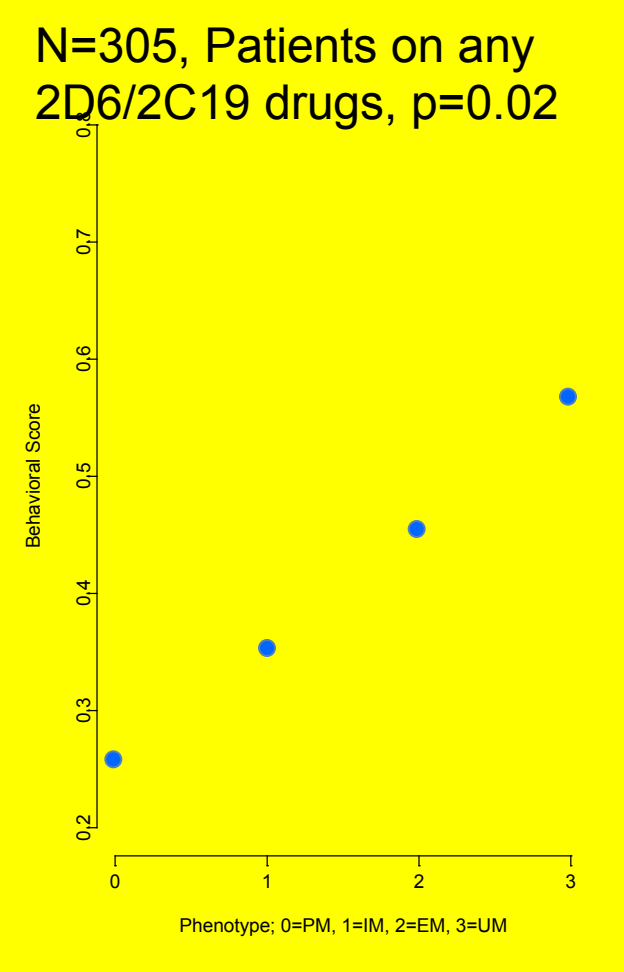
- Improved approach: minimize variability effect, place equal emphasis on each variable by using a weight-free index:
  - BIS = $\log (x_1+1) + \log (x_2+1) + \log (x_3+1)$

R.C.Elston. A weight-free index for the purpose of ranking or selection with respect to several traits at a time. The Biometric Society, Vol.19(1), March 1963.

Study Population

Characteristic		Children on CYP12D6/CYP2C19 psychotropics (n=305)
Age, median (25, 75 percentile)		13 (11,15)
Gender, female n (%)		147 (48%)
Primary Diagnosis		
	Mood disorders	161 (53%)
	Psychotic disorders	16 (5%)
	Disruptive behavior disorders	34 (11%)
	Anxiety disorders	58 (19%)
	Impulse control disorders	14 (5%)
	Adjustment disorders	3 (1%)
	Eating disorders	1 (0%)
	Pervasive developmental disorders	14 (5%)
	Miscellaneous	4 (1%)

Results: Genotype – Behavioral Intervention Score (BIS) Relationship (adjusted for age, sex, admitting GAF, diagnoses)



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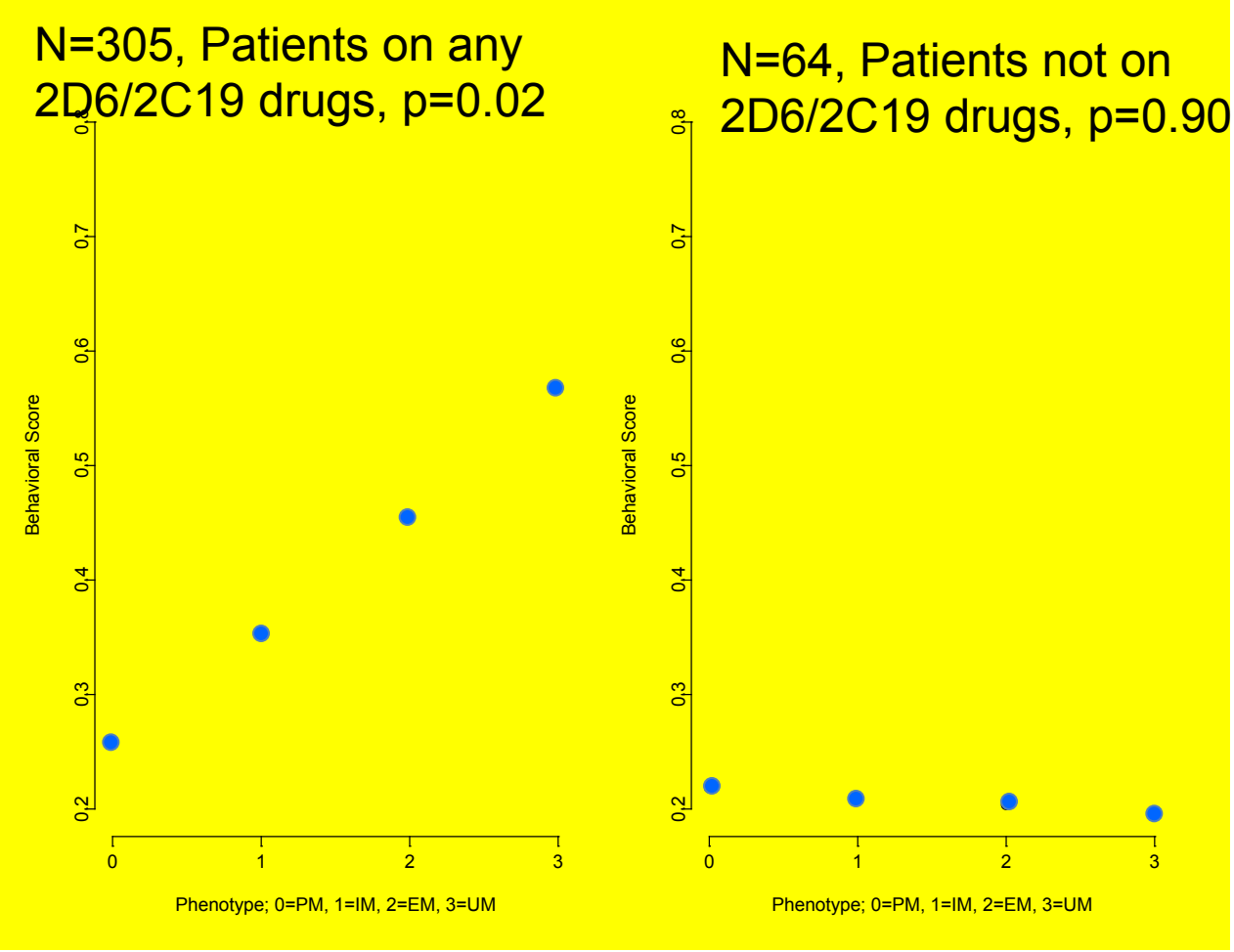


Not a disease effect

Relative Successes to date

- NeuroPsych drugs – CYP2D6, CYP2C19
- Codeine – CYP2D6 (Surgical/Pain service)
- Irinotecan – UGT-1A1 (CBDI)
- 6-mercaptopurine, azathioprine – TPMT (CBDI, GI)
- Warfarin – CYP2C9, VCOR1

Other (not pediatrics/CCHMC)

- Clopidogrel – CYP2C19, ABCB1
  - Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment (PREDICT)
- Tamoxifen – CYP2D6

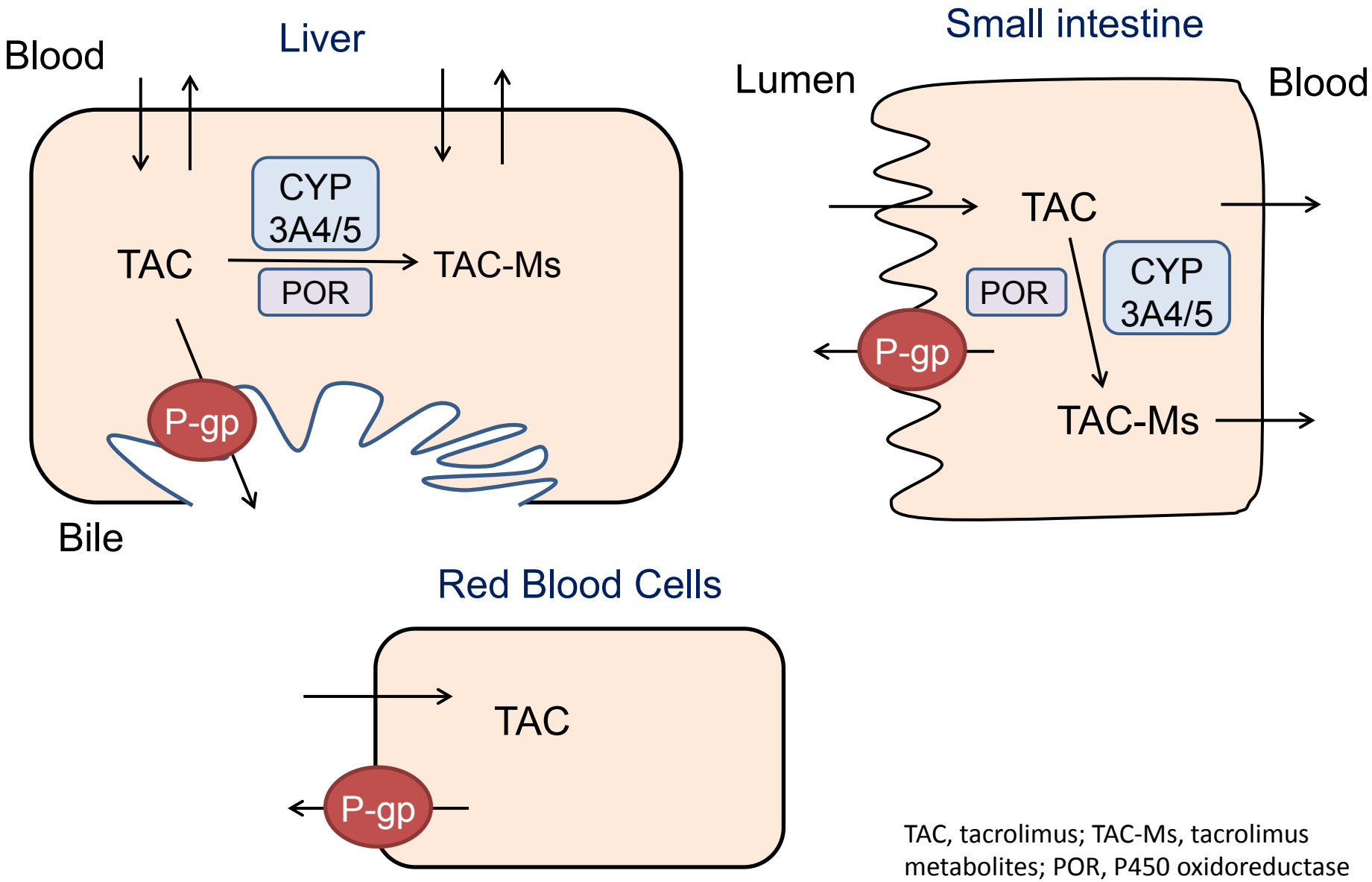
Janet Woodcock and Larry Lesko. Pharmacogenetics – Tailoring Treatment for Outliers. NEJM 2009:811-13.

Next steps at CCHMC – *Translational PGx projects*

Building on our EMR - Decision Support tools and outcomes studies with the Anderson Center

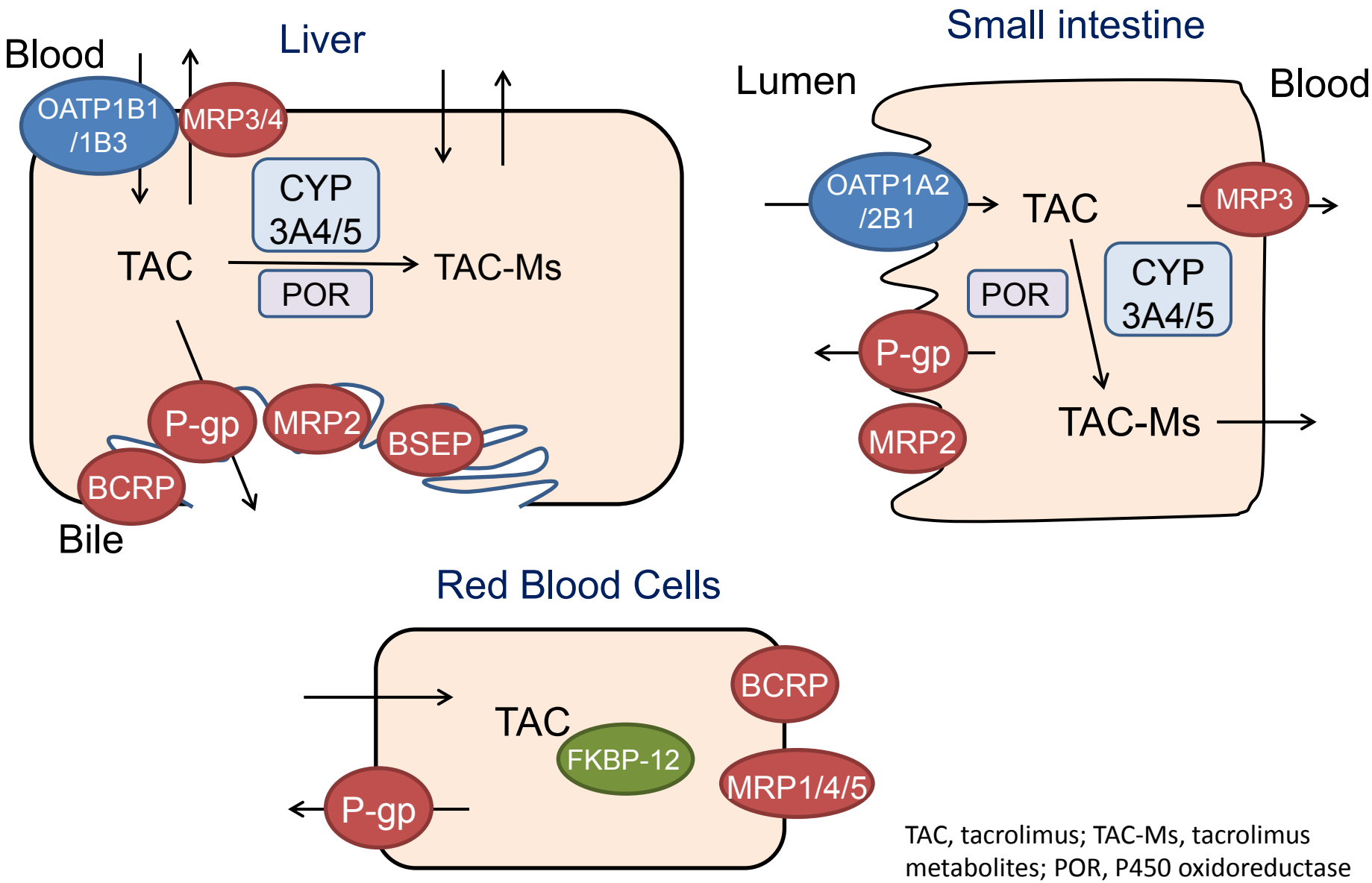
- Immunosuppressive drugs – CYP3A5*3, ABCB1
  - As proposed as part of our Genomic Medicine RFA application
- Immunomodulating drugs – UGT 2B7, 1A8/9
  - Mycophenolates PGx in Transplantation and cSLE
- Morphine - OPRM1, COMT and ABCB1 (OPRD1, TRPV1, 5HTT)
- Voriconazole – CYP2C19 (CYP3A4)
  - There is an ongoing pilot with our BMT group
- Technology: Affymetrics DMET or Illumina VeraCode ADME Core

Factors mediating tacrolimus disposition; Previous findings



TAC, tacrolimus; TAC-Ms, tacrolimus metabolites; POR, P450 oxidoreductase

Factors mediating tacrolimus disposition; Other pathways



TAC, tacrolimus; TAC-Ms, tacrolimus metabolites; POR, P450 oxidoreductase

Next steps at CCHMC – *Expansion of neuropsych drug panel*

5HT2C
ANK3-ANKRIN3
CACNAIC
COMT
CYP3A4
DRD2
MTHFY
SLC6A4

There is a small explosion of labs offering other tests in addition to CYP2D6 and 2C19. But it is unclear at this point what the correct interpretation should be.

Decision Support for Visit Planning

- ***Organize*** data for ***complex patients*** in a way that facilitates ***efficient*** and ***reliable*** clinical decision making

- ***Risk stratify*** patients for individual and ***population management***

- ***Automatically*** suggest indicated testing and therapies to providers

NEPHROLOGY: Pre-Visit Assessment and Care Patient:

MRN:		Overall Risk	Moderate		DOB:	2/18/1993	Age	19.0	DOT:	10/23/2009	Mths post Tx:	28.0	Years post Tx:	2.3	
Nxt Vst:	2/24/2012	Provider:	Hooper	Location:	BASE	Ht (cm):	166.7	Wt (kg):	101.6	BSA:	2.17	BMI:	36.561		
Lst Vst:	12/12/2012	Provider:	Hooper	Location:	BASE	Diagnoses:						Weight class:	Obese		

Immunosuppression

RISK			Current Therapy				Planned Deviations:		MD/RN Notes:			
Race:	Black/ African American		Last Four levels			Sirolimus	Immunosuppression:	NO				
Donor Type:	LRD		2/4/2012	12/10/2011	10/19/2011	9/16/2011	BP:	NO				
# HLA Mismatch:	0		6.1	3.1	5.1	7.2	Cholesterol:	NO				
Reject'n Episode:	Type	Date	Standard Deviation of the last 4 values:			1.7424						
									Fllw'd?	Helpfl?	Comments	Date
DSAs	Result:	Date:										
Infectious Disease Markers:			MMF	-	-	mg/BSA	-					
BK:	0	1/28/2012	Azathioprine	-	-	mg/kg	-					
EBV:	0	8/27/2001	Prednisone	-	-	mg/kg	-					
Immunologic Risk:	Low		Myfortic	720	-		-					

Cardiovascular Disease

Date:	Systolic	Diastolic	Systolic%ile	Diastolic%ile	BP Medications:	Dose	Suggested Action				
12/12/2011	127	64	80.5	25.2	Cozaar 50 mg q24h						
10/19/2011	105	55	1.6	8.1	Procardia XL 30 mg q24h						
9/12/2011	129	73	84.8	57							
									YES/ NO	YES/ NO	
Latest SBP Control:	In-Control										
Latest DBP Control:	In-Control										
BP Mgmt:	Below target w/ Rx										

Test:	Target:	12/10/2011	Cholesterol Medications:		Suggested Action				
Cholesterol	<200	147							
LDL	<130	98							
HDL	>45	26	Exercise Plan:						
Triglycerides	<200	117							
LDL/ Trig Mgmt:	No Dyslipidemia		Diet Plan:						
CV Stratification:	Only one RF controlled								

Behavior Mgmt

Area of Focus:		Suggested Action				
Self Mgmt:	Last SMA 12/12/11		YES/ NO	YES/ NO		
Psychology:			YES/ NO	YES/ NO		
Social Work:						
Adhere. Ctr:						
Behavior Mgmt Risk:	Low					

CKD

Test:	Result:		Suggested Action				
Cyst. C GFR:	56 ml/min	12/10/2011					
Proteinuria:	300	12/12/2011					
Creatinine:	1.4	10/19/2011					
	1.4	12/10/2011					
	1.4	2/4/2012	CKD Mgmt:	Monitoring up to date			

LABS

Test:	Test:	Test:	Test:	Test:	General Information/ Care Items
☐ Echo	☐ Testosterone	☐ CK	☐ Cyst. C	☐ Uric Acid	
☐ Lipids	☐ Renal Ultrasound	☐ LH	☐ 25-OHD	☐ Other	
☑ Hep B	☐ Fe Studies	☐ FSH	☐ BK	☐ Other	
☐ DSAs	☐ Liver Profile	☐ PTH	☑ EBV	☐ Other	

DK Hooper, 2011

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Nxt Vst:	2/24/2012	Provider:	Hooper	Location:	BASE	Ht (cm):	166.7	Wt (kg):	101.6		BSA: 2.17	BMI:	36.561	
Lst Vst:	12/12/2012	Provider:	Hooper	Location:	BASE	Diagnoses:						Weight class:	Obese	

Risk

Immunosuppression

RISK

Race:	Black/ African American
Donor Type:	LRD
# HLA Mismatch:	0
Reject'n Episode:	Type / Date
DSAs	Date:
Infectious Disea	
BI	1/28/2012
EBV	8/27/2001
Immunologic Ri:	Low

Current Therapy

Last Four levels	Sirolimus		
2/4/2012	12/10/2011	10/19/2011	9/16/2011
6.1	3.1	5.1	7.2

Standard Deviation of the last 4 values: 1.7424

Drug	Total Daily Dose (mg)	Current target or corrected dose		Protocol target/dose
Tacrolimus	-	-	ng/ml	-
Sirolimus	3	4-7	ng/ml	4-7
MMF	-	-	mg/BSA	-
Azathioprine	-	-	mg/kg	-
Prednisone	-	-	mg/kg	-
Myfortic	720	-		-

Planned Deviations:

Immunosuppression:	NO
BP:	NO
Cholesterol:	NO

MD/RN Notes:

Cardiovascular Disease

Date:	Diastolic	Systolic%ile	Diastolic	Medications:	Dose
12/12/2011	64	80.5	25.2	ar 50 mg q24h	
10/19/2011	55	1.6	8.1	ardia XL 30 mg q24h	
9/12/2011	73	84.8	57		
Latest SBP Cont	In-Control	Echo Results:	(date		
Latest DBP Cont	In-Control	ABPM Results:	(date		
BP Mgmt:	w target w/ Rx	Home BP:	(date sta		

Test:	12/10/2011
Cholesterol	147
LDL	98
HDL	26
Triglycerides	117
LDL/ Trig Mgmt:	Dyslipidemia
CV Stratificatior	ne RF controlled

Exercise Plan:

Diet Plan:

esterol Medications:

Behavior Mgmt

Area of Focus:	
Self Mgmt:	12/12/11
Psychology:	
Social Work:	
Adhere. Ctr:	
Behavior Mgmt Risk:	Low

CKD

Test:	Result:	
Cyst. C GFR:	56 ml/min	12/10/2011
Proteinuria:	300	12/12/2011
Creatinine:	1.4	10/19/2011
	1.4	12/10/2011
	1.4	2/4/2012

CKD Mgmt: Monitoring up to date

Current Therapy

Suggested Action

Suggested Action	Fllw'd?	Helpful?	Comments	Date
Sched Echo	YES/ NO	YES/ NO		
SMA D e dietician	YES/ NO	YES/ NO		
Transition F ndra	YES/ NO	YES/ NO		

Suggested Action

Provider Response

LABS

Test:	Test:	Test:	Test:	Test:	General Information/ Care Items
☐ Echo	☐ Testosterone	☐ CK	☐ Cyst. C	☐ Uric Acid	
☐ Lipids	☐ Renal Ultrasound	☐ LH	☐ 25-OHD	☐ Other	
☑ Hep B	☐ Fe Studies	☐ FSH	☐ BK	☐ Other	
☐ DSAs	☐ Liver Profile	☐ PTH	☑ EBV	☐ Other	

DK Hooper, 2011

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Lst Vst:	12/12/2012	Provider:	Hooper	Location:	BASE	Diagnoses:					Weight class:	Obese	

Immunosuppression

RISK			Current Therapy				Planned Deviations:		MD/RN Notes:
Race:	Black/ African American		Last Four levels	Sirolimus			Immunosuppression:	NO	
Donor Type:	LRD		2/4/2012	12/10/2011	10/19/2011	9/16/2011	BP:	NO	
# HLA Mismatch:	0		6.1	3.1	5.1	7.2	Cholesterol:	NO	
Reject'n Episode:	Type	Date	Standard Deviation of the last 4 values:			1.7424			

Drug	Total Daily Dose (mg)	Current target or corrected dose		Protocol target/dose	Suggested Action	Fllw'd?	Helpfl?	Comments	Date
Tacrolimus		-	ng/ml	-					
Sirolimus	3								
MMF	-								
Azathioprine									
Prednisone	-								
Myfortic	720	-		-					

DSAs	Result:	Date:

Infectious Disease Markers:		
BK:	0	1/28/2012
EBV:	0	8/27/2001
Immunologic Risk:	Low	

Cardiovascular Disease

Date:	Systolic	Diastolic	Systolic%ile	Diastolic%ile
12/12/2011	127	64	80.5	25.2
10/19/2011	105	55	1.6	8.1
9/12/2011	129	73	84.8	57

BP Medications:	Dose
Cozaar	50 mg q24h
Procardia XL	30 mg q24h

Suggested Action

Latest SBP Control:	In-Control	Echo Results: (date)
Latest DBP Control:	In-Control	MRI Results: (date)
BP Mgmt:	Below target w/ Rx	Home BP: (date started)

Suggested Action: Sched Echo — YES/ NO — YES/ NO

Test:	Target:	12/10/2011
Cholesterol	<200	147
LDL	<130	98
HDL	>45	26
Triglycerides	<200	117
LDL/ Trig Mgmt:	No Dyslipidemia	
CV Stratification:	Only one RF controlled	

Cholesterol Medications:

Exercise Plan:

Diet Plan:

Suggested Action

Behavior Mgmt

Area of Focus:	
Self Mgmt:	Last SMA 12/12/11
Psychology:	
Social Work:	
Adhere. Ctr:	
Behavior Mgmt Risk:	Low

Suggested Action

SMA	Diet/exercise	dietician	YES/ NO	YES/ NO
Transition	F/U with Sondra		YES/ NO	YES/ NO

CKD

Test:	Result:	
Cyst. C GFR:	56 ml/min	12/10/2011
Proteinuria:	300	12/12/2011
Creatinine:	1.4	10/19/2011
	1.4	12/10/2011
	1.4	2/4/2012
CKD Mgmt:	Monitoring up to date	

Suggested Action

LABS

Test:	Test:	Test:	Test:	Test:	General Information/ Care Items
☐ Echo	☐ Testosterone	☐ CK	☐ Cyst. C	☐ Uric Acid	
☐ Lipids	☐ Renal Ultrasound	☐ LH	☐ 25-OHD	☐ Other	
☑ Hep B	☐ Fe Studies	☐ FSH	☐ BK	☐ Other	
☐ DSAs	☐ Liver Profile	☐ PTH	☑ EBV	☐ Other	

Color Coded Risk Stratification

Color Coded Suggested Actions

DK Hooper, 2011

Limitations

- Outside of the EMR (distribution requires email, photocopies, etc…)
- Requires manual data input (dual entry) from the EMR (time, resources, human error)
- Does not incorporate pharmacokinetic data
- Limited information on adherence

What if we had…

…***pharmacokinetic*** data

and…

…***adherence*** data

and…

…protocol recommended drug level targets

and…

…patient reported ***outcomes*** (side effects)

and…

…***passive*** patient reported outcomes…

…all in the same place?

Research Questions

- How does visit planning with decision support impact outcomes?
  - Adherence
  - Rejection of transplanted kidney
  - Survival of transplanted kidney
  - Cost

Research Questions

- Can we also incorporate patient reported outcomes (social networking, smart phone apps etc…)? Yes & underway…
- How can these same principles be applied to other chronic disease populations (adults and children)?
  - Other solid organ transplant
  - Diabetes
  - Hypertension
  - Any chronic condition

Genetic Pharmacology Service

- Vision: To improve the management of childhood disorders by:
  - Systematic integration of genotypic, phenotypic, biologic, psychosocial, and environmental variables
  - Identify patients genetically predisposed to
    - Toxicity & Non-response
    - Treat these patients with different doses alternative medications
  - Multidisciplinary approach to analyze impact of these different factors on clinical outcome and educate health care providers in their use

Clinical Services (Human Genetics):

Technology Available:

- Targeted DNA genotyping
- RT-PCR
- Quantitative PCR
- Southern Blot analysis
- Sanger Sequencing
- AB Low Density Array
- Affymetric resequencing array
- NextGen Platforms
  - Raindance Target Enrichment
  - HiSeq2500 & MiSeq

>60 tests offered:

- Primary Immunodeficiencies
- Hearing Loss
- Pharmacology Genetic Services
- Fatty Acid Oxidation Disorders
- Inherited Liver Diseases
- Lysosomal Storage Diseases
- Oncology Services
- Thrombophilic Condition
- Mitochondrial diseases
- Hemoglobin defects

Molecular Genetics Laboratory | Diagnostic Laboratories

Clinical NextGen Tests* Offered at CCHMC

- **OtoSeq** Hearing Loss Panel
  - 23 genes, sensorineural hearing loss

- **MetaboSeq** Fatty Acid Oxidation Disorder Panel
  - 19 genes, fatty acid oxidation metabolic pathway

* Any <u>results reported</u> are 1st confirmed by Sanger sequencing

Clinical NextGen Tests for 2013

Immunodeficiency Panels

- Severe Combined Immunodeficiency(**SCID**)-30 genes
- Hemophagocytic Lymphohistiocytosis(**HLH**)- 14 genes
- Autoimmune Lymphoproliferative Syndrome (**ALPS**)-5 genes
- Severe Congenital Neutropenia (**SCN**)-6 genes
- Mendelian Susceptibility to Infection panel (**MSI**)-19 genes
- Common Variable Immunodeficiencies (**CVID**)- 15 genes
- Autoimmune Disorders (**IBD/IPEX/AIRE**)- 7 genes
- Chronic Granulomatous Disease (**CGD**)- 7 genes
- Familial Periodic Fever (**PFP**)- 6 genes
- Hyper-IgM Syndrome(**HIGM**)- 14 genes
- Hyper IgE Syndrome (**HIGE**)- 3 genes

Clinical NextGen Tests for 2013

- Hematology/Oncology
  - Fanconi Anemia (14 genes)
  - Diamond-Blackfan Anemia(**DBA**)-10 genes
  - Bone Marrow Failure syndrome(**BMF**)- 25 genes
  - Chromosomal Breakage Disorders (**CBD**)- 7 genes
  - Erythrocyte Cytoskeleton Disorders(**ECD**)- 24 genes
  - TMA-aHUS panel- 15 genes
  - Platelet disorder panel- 36 genes
- Dermatology
  - Dyskeratosis Congenita (**DKC**)- 7 genes
  - Epidermolysis Bullosa (**EB**)- 24 genes
- Ophthalmology
  - Eye disorder panel (**EyeSeq**)- 40 genes

Next Steps -- *Whole Exome Sequencing* as a clinical test.

- Greater Cost of targeted sequencing will lead to whole exome sequencing.
- More accurate, highly redundant coverage will make Confirmation by Sanger sequencing unnecessary.
- When target negative, Query the exome.
- Best practices for Incidental Results.

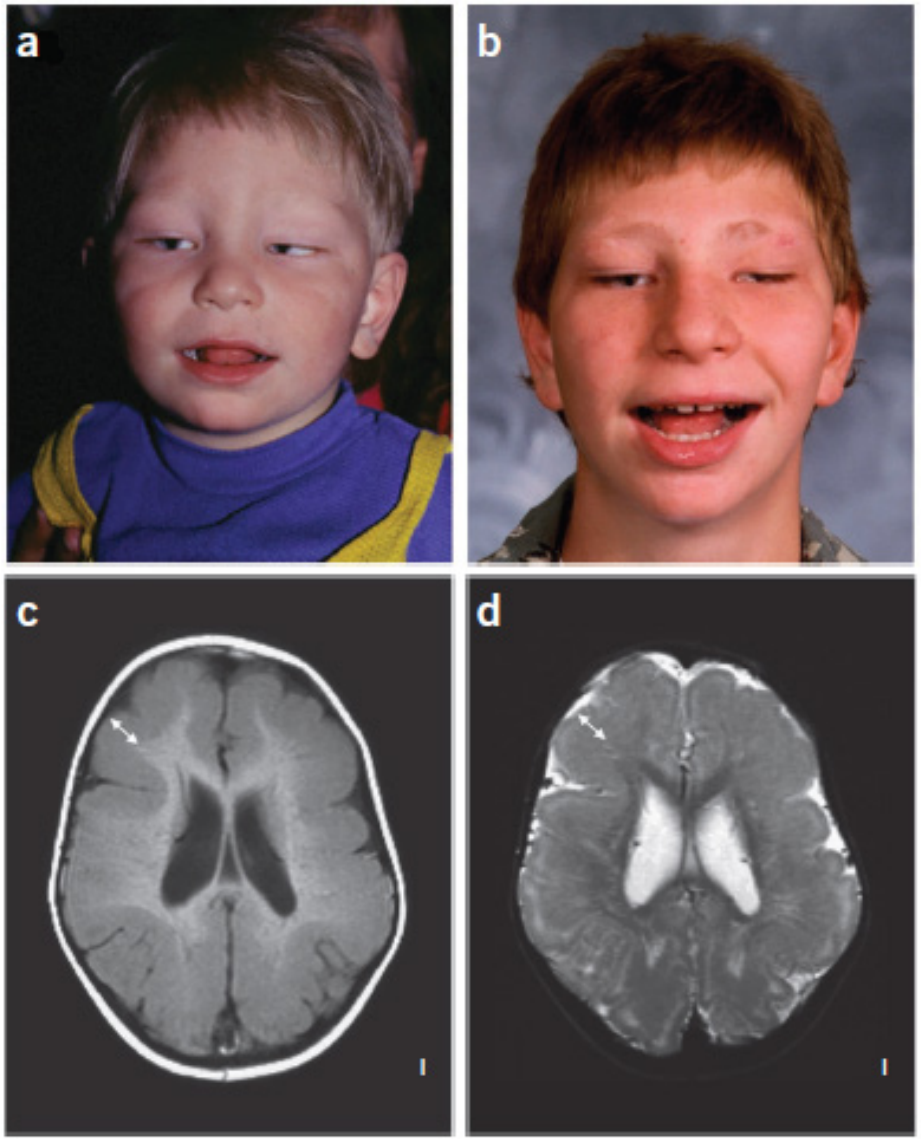
CCHMC 2012 Exome Sequencing: Discovery &/vs. Clinical Utility

366 subjects from 122 trios

- Systemic Lupus Erythematosus (**SLE**) (38)
- Juvenile Idiopathic Arthritis (**JIA**) with Macrophage Activation Syndrome (**MAS**) (48)
- Eosinophilic Esophagitis (18)
- Diaphragmatic Hernia (9)
- Disseminated Staphylococcus after Osteomyelitis (4)
- Tracheal Ring Deformity (3)
- Congenital Neutropenia (1)
- Situs Inversus (1)
- Idiopathic Liver Failure, Cloacal Extrusion, Esophageal Atresia, Microgyria, Early Childhood Severe Obesity

Baraitser Winter Syndrome

Riviere et al., Nature Genetics, 2012



Intellectual Disability
Hearing Loss
Seizures
Short Stature
Microcephaly (postnatal)
Pachygyria (lissencephaly)
Facial Dysmorphia
Ocular Colobomata

- 18 of 18 ***de novo variants*** (or rare variants) in actin genes: **ACTB** (10) or **ACTG1** (8)
- 11 proven *de novo*
- **Neural cell migration defect**

Parallel "next generation" Sequencing

- Advantage: Massive amounts of sequence

Exome:	2 Gb	60,000 variants
Genome:	100 Gb	3,000,000 variants

- Problems:
  - Unreliable sequence
    - Error in the sequence & alignment
    - Interference across replicated regions
    - Incomplete sequence
  - Analysis is a nightmare
    - Too much sequence and way too many variants
  - Too expensive

Exome Sequencing: Critical Infrastructure

- Genetic Counseling… *(expertise)*
- Technical capacity… *(expertise)*
  - Next generation sequencing
  - Confirmation
- Informatics… *(expertise)*
  - Processing to annotated file
  - Preparation of files for interpretation
  - Preservation
- Interpretation … *(expertise)*
  - Return of results (phenotype & incidental)
  - Future re-use
- Financing… *(courage)*

Whole Exome Sequencing
Clinical Application

Begin – Phenotypes with literature support

- Severe Intellectual Disability (20-40%)
- Autism (~15%)

- Then…
  - …many, many rare conditions.
  - …many uncharacterized common conditions.

Clinical Whole Exome Sequencing at CCHMC

Plans

Diagnostic & Prognostic Genomics

Past	Present	Future
Sanger	Sanger	? Sanger
	Array	? Array
	Targeted NG	? Targeted NG
	- Gene Sets	**Exome**
	- almost Exome	***Whole GENOME***
		other genomics*

**Epigenetics, Expression, Metabolomics, ChIP-Seq, Proteomics, Chromatin Conformation, etc…*

Epigenome-wide association data in RA

- Liu et al, *Nat Genetics*, on line 2013.
- Causal Inference Test for methylation of peripheral blood mononuclear cells in Rheumatoid Arthritis.

- Single nucleotide polymorphism (SNP) (p<10E-14)

(DRB1_AA104_E2_326559926_AE)

Differentially Methylated Place (DMP)

(cg16609995 – *PBX2*) (p<10E-8)

CIT p<10E-15

Rheumatoid arthritis (RA)

Causal Inference Test

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Thank you

Immunosuppression | Cardio Disease | CKD | Behavior Mgmt | Problem List | Medication List

Project	MEMS-CD	MON-STAT	WARNING	ADH-LVL	CURR-DRUG	CURR-REGIMEN	DRUG-HOLIDAY	EXTRA-DOSE
10518	315426	on		6.666667%	CellCept		The treatment has been interrupted by the patient for more than 2 consecutive days (estimated over intervisit): 1 times	
10518	315427	on		6.666667%	CellCept		The treatment has been interrupted by the patient for more than 2 consecutive days (estimated over intervisit): 1 times	

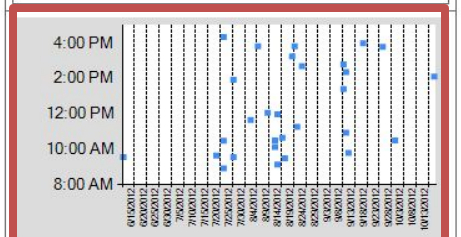
RISK

Select a MEMS cap for ADH. details: 315426

315426

MEMS-CD	Date	DRUG	MON-ID	Shape	Time	Type
315426	10/17/2012 2:07:00 PM	188	0	circle	14.12	normal
315426	10/1/2012 10:31:00 AM	172	0	circle	10.52	normal
315426	9/26/2012 3:47:00 PM	167	0	circle	15.78	normal

> | >>



October 2012

Su	Mo	Tu	We	Th	Fr	Sa
30	1 (1)	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17 (1)	18	19	20
21	22	23	24	25	26	27
28	29	30	31	1	2	3
4	5	6	7	8	9	10

** (N) represents the number of doses.

Self-Management Assessment:

Behavior Mgmt Risk: Low

Behavior Mgmt Risk

CURRENT THERAPY

PSYCH | SOC WK

Is Ad. Ctr/Psychology Involved? Yes No

Current Action Plan:

SUGGESTED ACTIONS

Actions for Ad. Ctr/Psych?

Option 1

Actions for Social Worker:

Option 1

Stage of Action Planning

preloaded action 1 Accept?

Other:

Responsible Provider

preloaded action 1 Accept?

Other:

Other Suggestions

Plan Notes:

Update the Current Plan | Save as New Plan with Today's Date

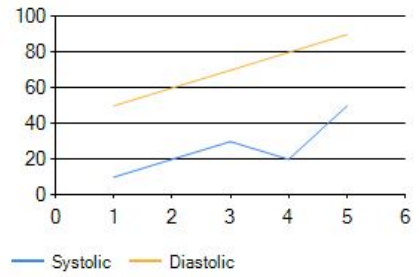
Immunosuppression | Cardio Disease | CKD | Behavior Mgmt | Problem List | Medication List

RISK

Smoking Exposure: 10 years exposure to s

Family History: Direct relatives have ca

Blood Pressure: (give last 5 outpatient measures)



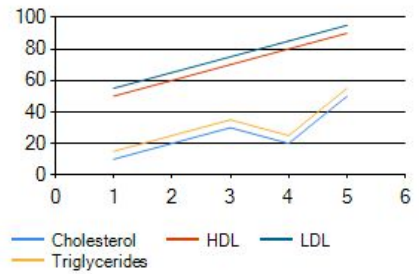
Echo Results:

ABPM Results:

Does patient have a home BP log? ☐

BP Mgmt Risk Level:

Cholesterol:



Cholesterol Risk Level:

Cardiovascular Risk: High

Cardiovascular Risk

CURRENT THERAPY

Blood Pressure Meds

Drug	Daily Dose
Diuretics	Dose1
captopril (Capoten)	Dose2

Exercise Plan:

New exercise effective 9/1/2012. Increase daily activity time to 30 minutes.

Diet Plan:

A healthy food plan.

Cholesterol Meds:

Drug	Daily Dose
Lipitor (atorvastatin)	10mg once daily
Colestid (colestipol)	2-16 grams

SUGGESTED ACTIONS

Blood Pressure Medication

Drug	Suggested Action
Enalapril 5 mg q24h	Suggested: BP ☐ Accept? Overwrite:
Norvasc 10 mg q24h	Suggested: BP ☐ Accept? Overwrite:
Atenolol 25 mg q24h	Suggested: BP ☐ Accept? Overwrite: -

Cholesterol Medication

Other Suggested Actions:

Require regular physical check up.

Plan Notes:

Update the Current Plan | Save as New Plan with Today's Date

Outline

- Intro
- Patient population / special characteristics
- Existing Genomic Services
  - Sanger sequencing
    - CYP2D6 & pharmacogenomics
    - How many? What do we send out?
  - Cytogenetics

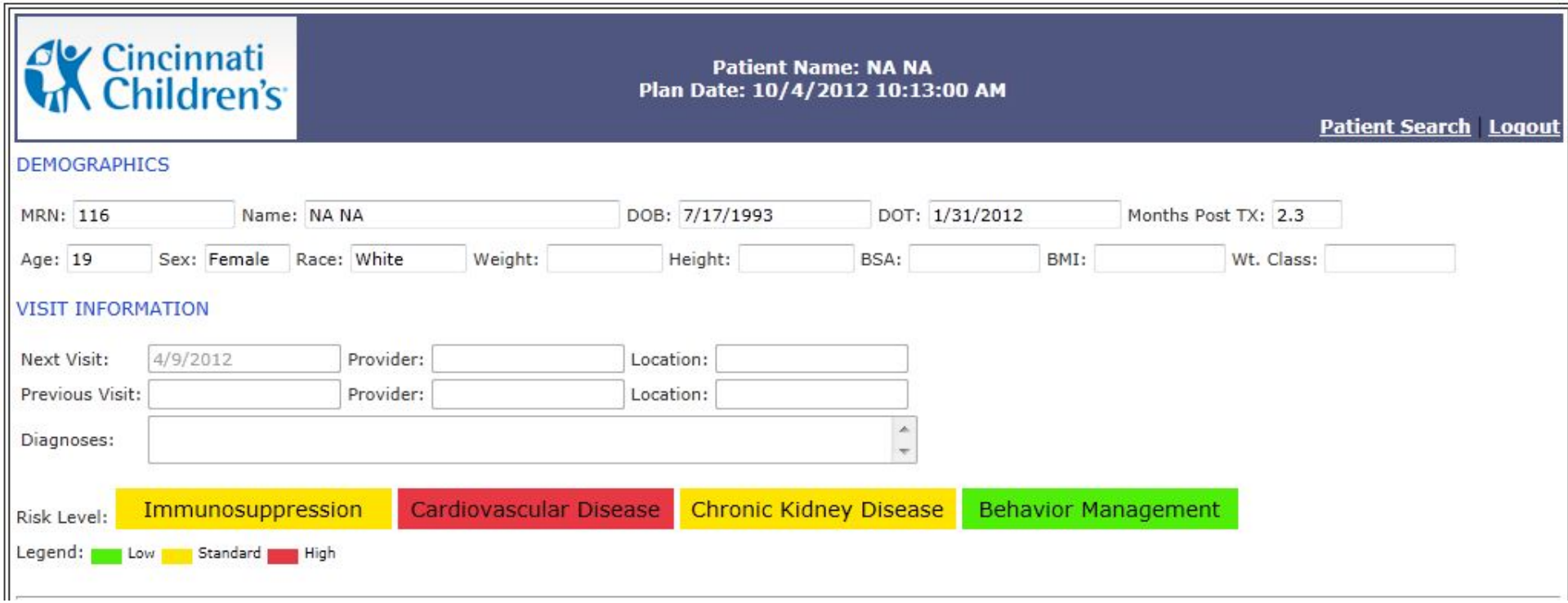
- Adapt targeted gene analysis to next generation sequencing
  - Kejian's plans

- Whole exome sequencing
  - Intellectual disability
  - Idiopathic severe disease

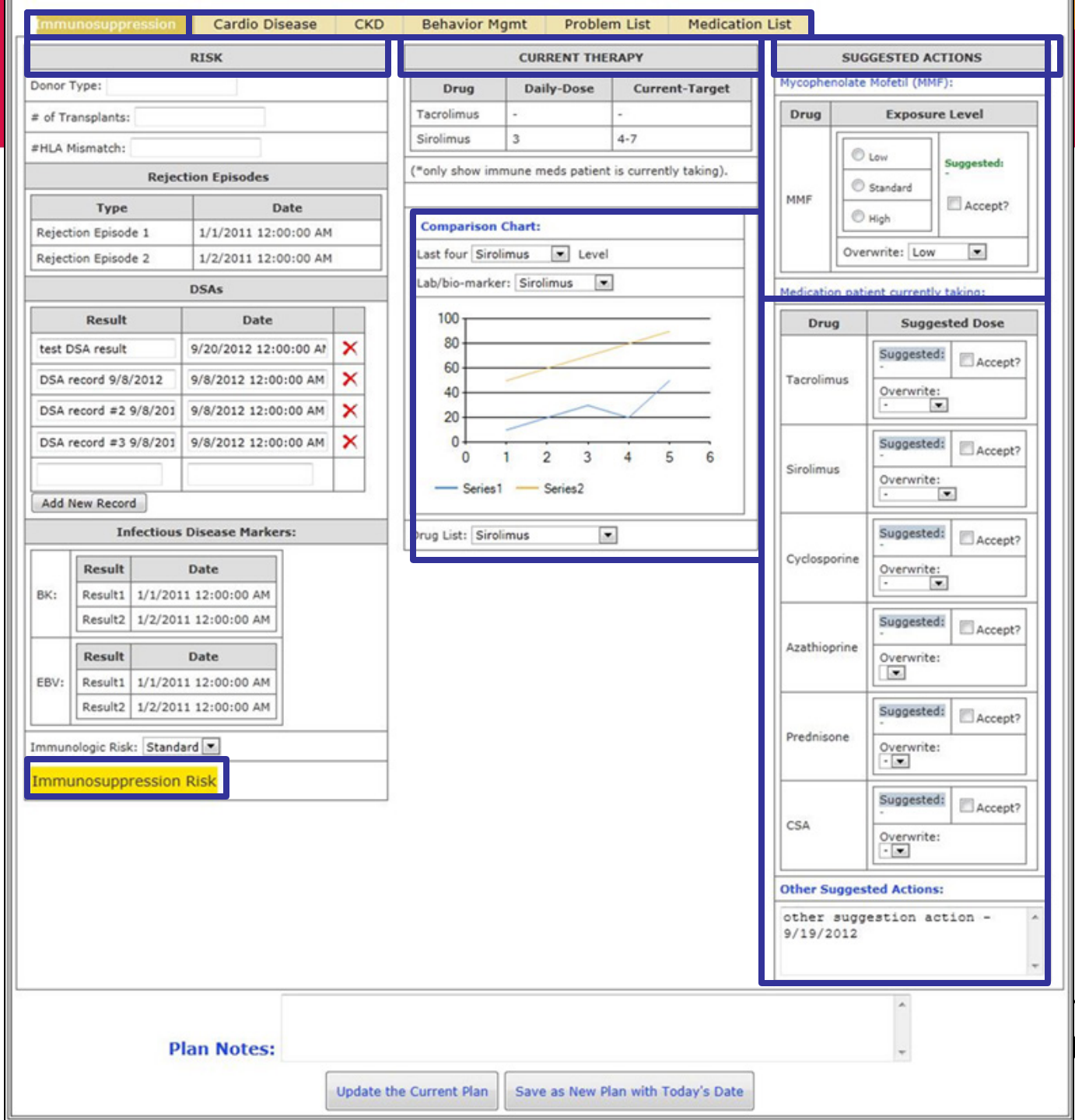
- What are we missing?
  - Expression analyses
  - DNA methylation
  - Histone marks
  - Any manner of ChIP-Seq analyses.

WHAT WOULD IT LOOK LIKE?

Cincinnati Children's



Cincinnati Children's



cincinnati children's