

Development of In-house PGx Testing at Children's Mercy

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Children's Mercy Kansas City

- Non-profit independent children's hospital
- Founded in 1897
- 8,000+ employees
- 800+ faculty members
- 3,000+ nurses
- 1,000+ allied health professionals
- More than 700 volunteers

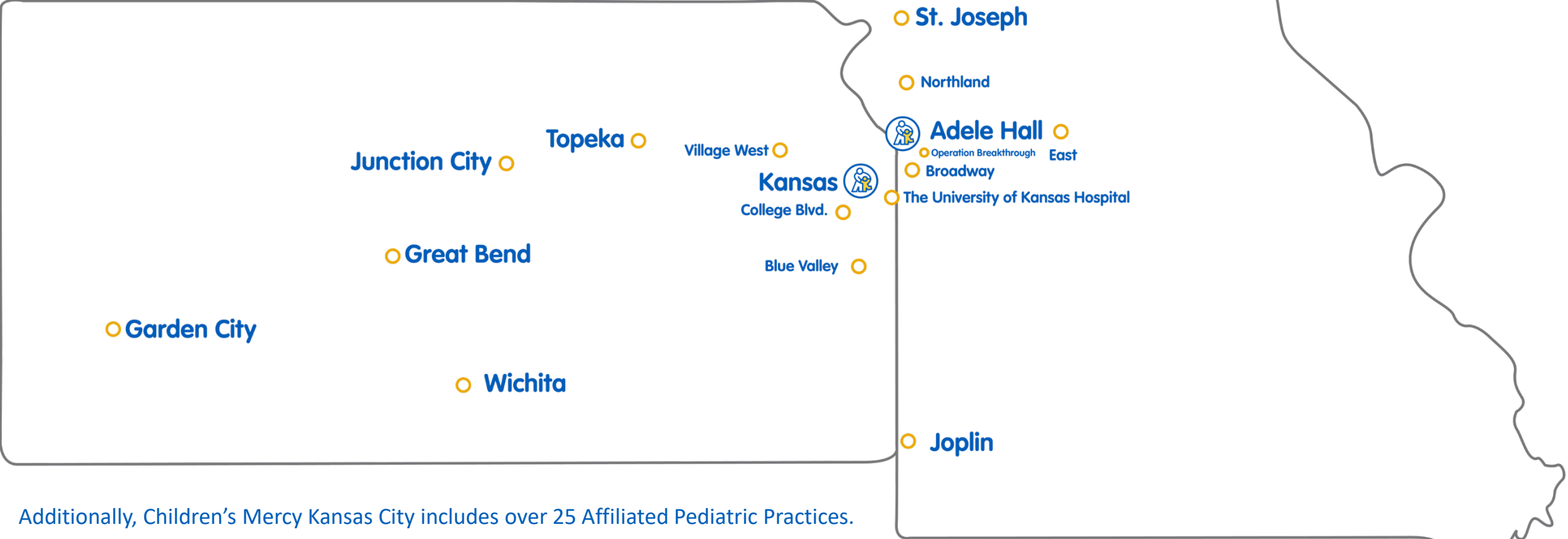


The Region's Pediatric Health System of Choice

- 390 beds
- 335,734 outpatient visits
- 202,496 ER/UC visits
- 14,345 admissions
- 19,469 surgeries
- 5,942 transports



Locations



Additionally, Children's Mercy Kansas City includes over 25 Affiliated Pediatric Practices.



Leaders in Clinical Genomics

- 5-base HiFi long read sequencing used clinically for diagnosis
- Cancer patients get short read exome sequencing of germline and tumor (long read in validation)
- Genomic Answers for Kids research study



families
enrolled



individuals
enrolled



genomic
analyses



gigabases
sequenced*



diagnoses
from study

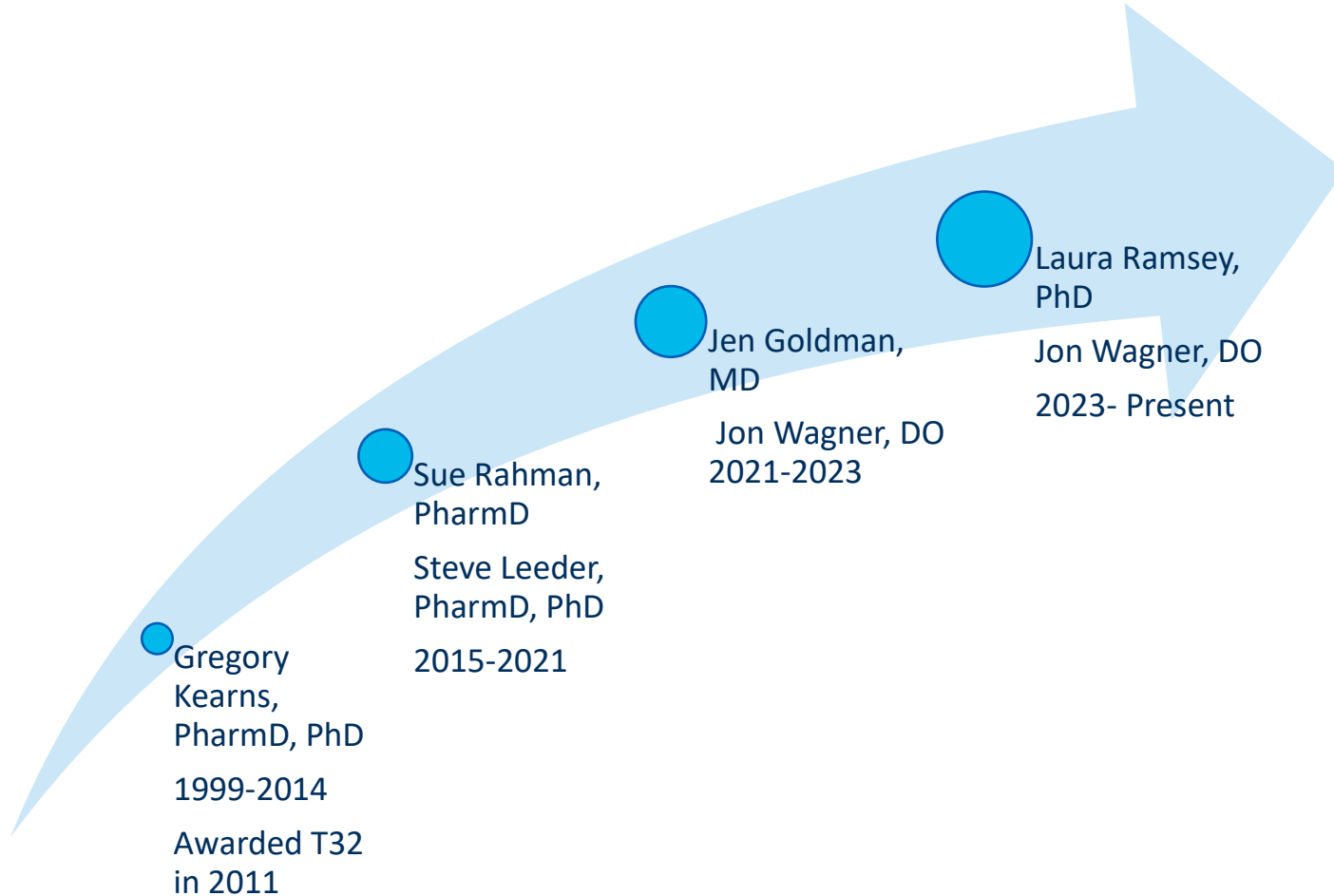


Leaders in Pharmacogenetics

- Home of PharmVar
- Andrea Gaedigk (author on 14 CPIC guidelines)
- Steve Leeder (author on 5 CPIC guidelines)
- Laura Ramsey (author on 4 CPIC guidelines)
- GOLDILOKs clinic
- Pediatric Clinical Pharmacology Fellowship



History of Clinical Pharmacology Fellowship Training at CMH



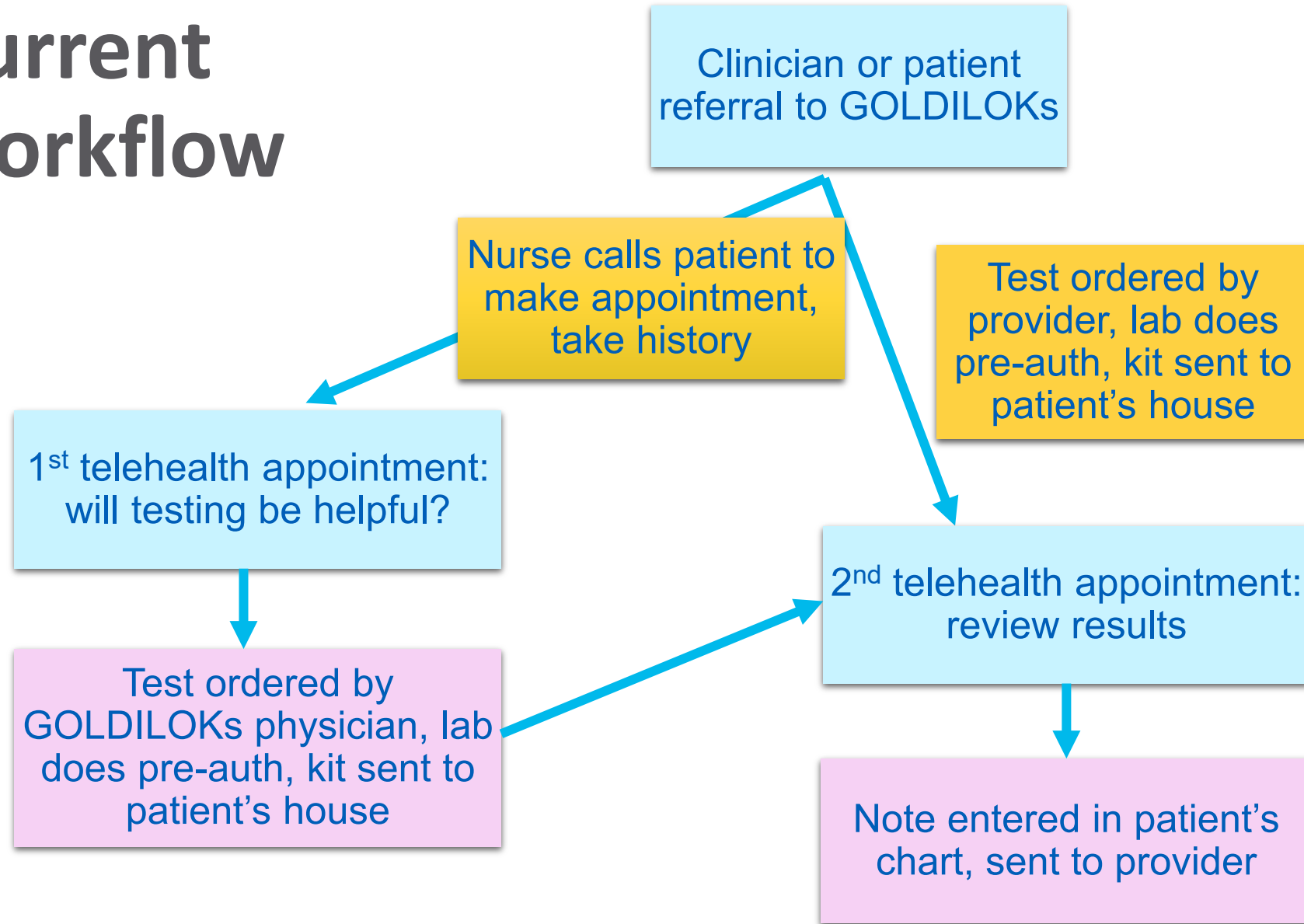
- Fellowship training started in 1999
- Total of 24 fellows trained since 1999
- 17 MD/DO, 4 PharmD/PhD, 3 PharmD, 1 APRN
- Total of 18 fellows trained since CMH awarded NICHD T32 grant in 2011
- 11 Subspecialities trained



GOLDILOKs Clinic

- Genomic and Ontogeny-Linked Dose Individualization and cLinical Optimization for KidS Clinic
- Pediatrician & pharmacist have telehealth visit with patients/families
- Nurse, social worker, PGx experts involved
- External testing labs

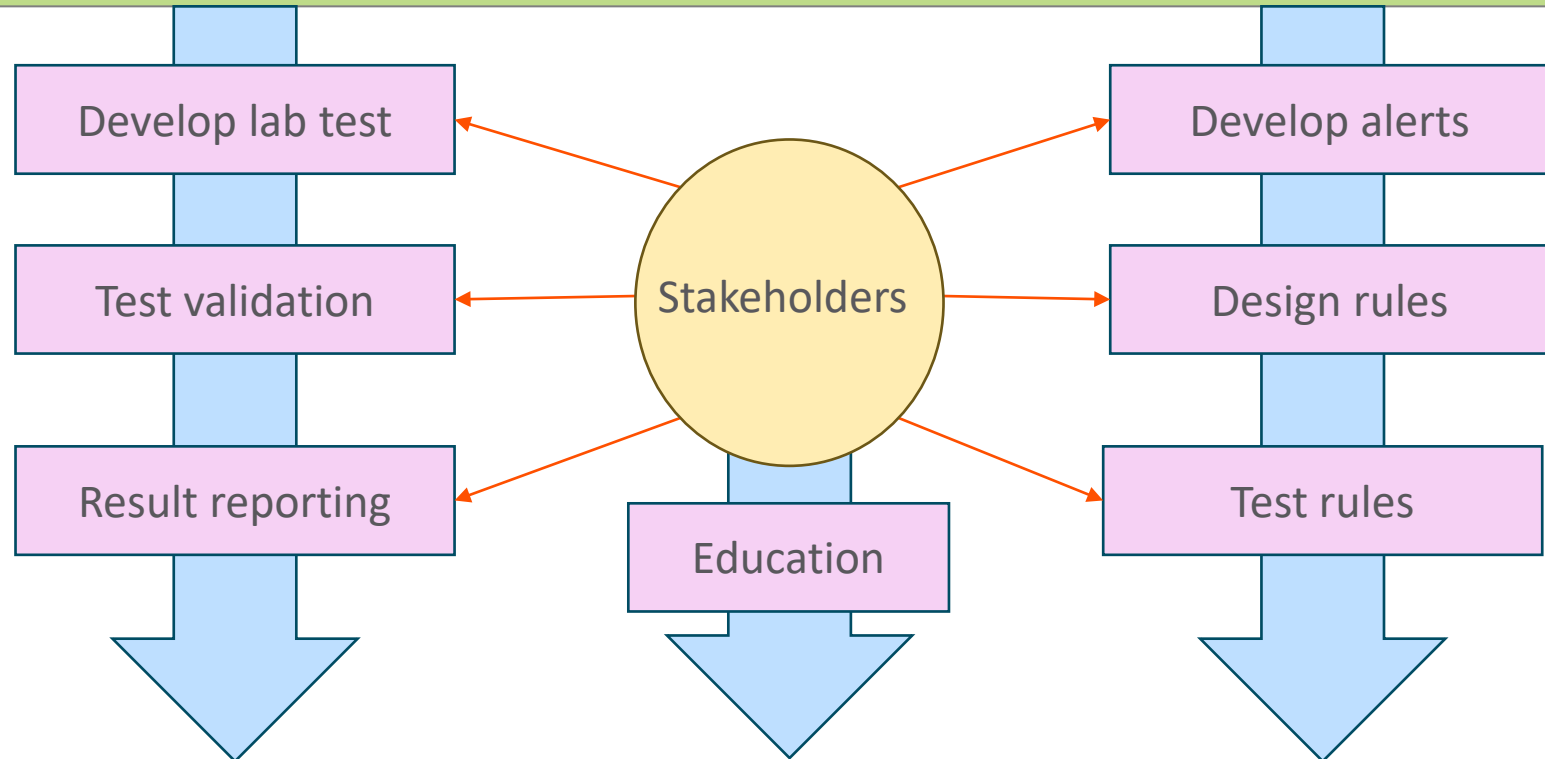
Current workflow



Opportunity to build in-house PGx testing and clinical decision support

- Clinical genomics expertise
- Pharmacogenetics expertise
- Clinician buy-in
- Informatics team buy-in
- Service model
- Commercial lab stopped accepting samples from us

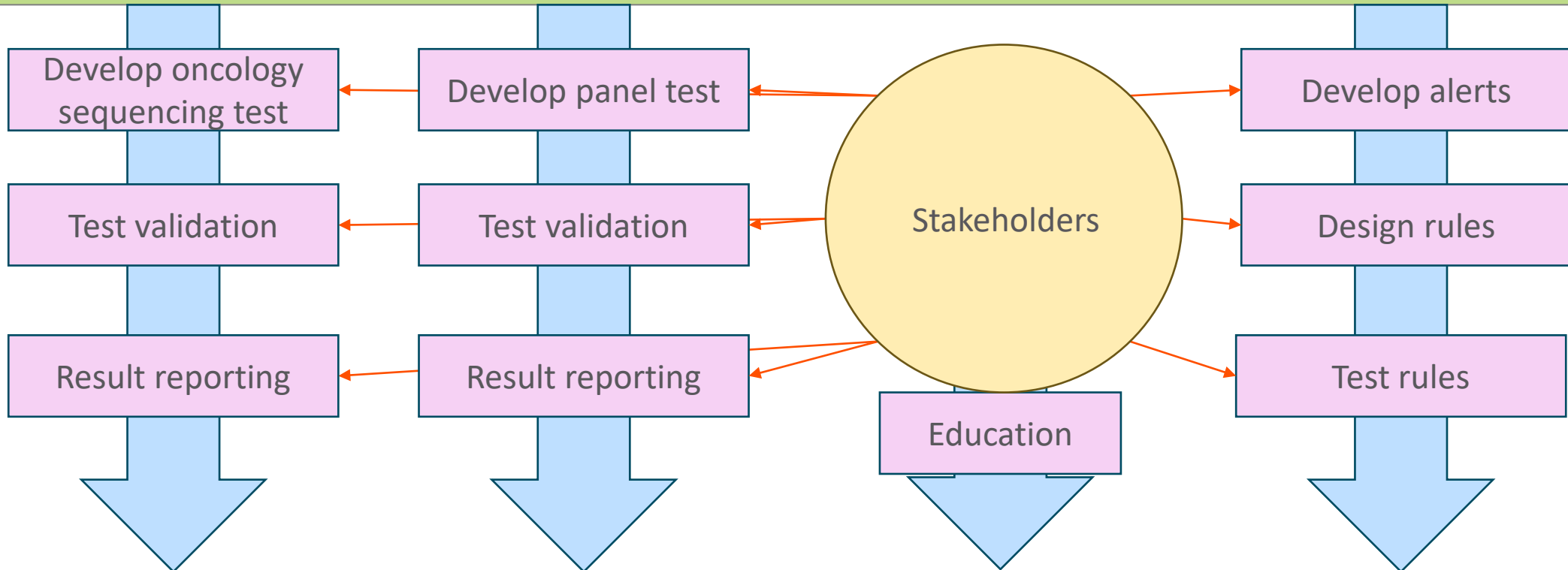
PGx Implementation Current State



PGx Implementation Future State



PGx Implementation Current State



PGx Implementation Future State



Oncology PGx

- *TPMT* testing performed for leukemia patients by external lab
- *NUDT15* testing performed occasionally
- Director of Molecular Oncology & Asst Lab Director wanted to collaborate to offer *TPMT* & *NUDT15* testing from 300x short read whole exome sequencing (WES)
- Used Illumina DRAGEN™ Star Allele Caller on 10 Coriell cell line samples covering 7 *NUDT15* alleles and 6 *TPMT* alleles, 100% concordant with GeT-RM calls

Oncology PGx CDS

Menu

- MPages
- Orders + Add
- MAR
- MAR Summary
- RxStation Medication Queuing
- CS Waste Report
- Results Review
- Oncology
- Microbiology Viewer
- PowerNote + Add
- Forms
- Documents
- I-View
- Growth Chart
- Clinical Research

Results Review

Lab Radiology Recent Results Selected Results - 12 Months

Flowsheet: Lab View Level: Lab View

Navigator

- Cancer Pharmacogenomics

Show more results

Lab View

- Cancer Pharmacogenomics NGS
- Cancer Pharmacogenomics NGS Final Re
- TPMT Genotype
- TPMT Phenotype
- NUDT15 Genotype
- NUDT15 Phenotype



Phenotype Alert

6-mercaptopurine can be affected by a patient's TPMT and NUDT15 phenotype. This patient is predicted to be TPMT intermediate metabolizer and NUDT15 intermediate metabolizer. This patient is at risk for myelosuppression with normal starting dose of 6-mercaptopurine. Consider starting 6-mercaptopurine at a reduced starting dose if normal starting dose is 75 mg/m²/day or 1.5 mg/kg/day (e.g., start at 22.5-60 mg/m²/day or 0.45-1.2 mg/kg/day) based on degree of myelosuppression and specific guidelines. Allow 2-4 weeks to reach steady-state after dose adjustment. If myelosuppression occurs, and depending on other therapy, dose reduction should be on reducing mercaptopurine over other agents. If normal starting dose is already <75mg/m²/day or < 1.5mg/kg/day, dose reduction may not be recommended. Please consult a clinical pharmacist for more information.

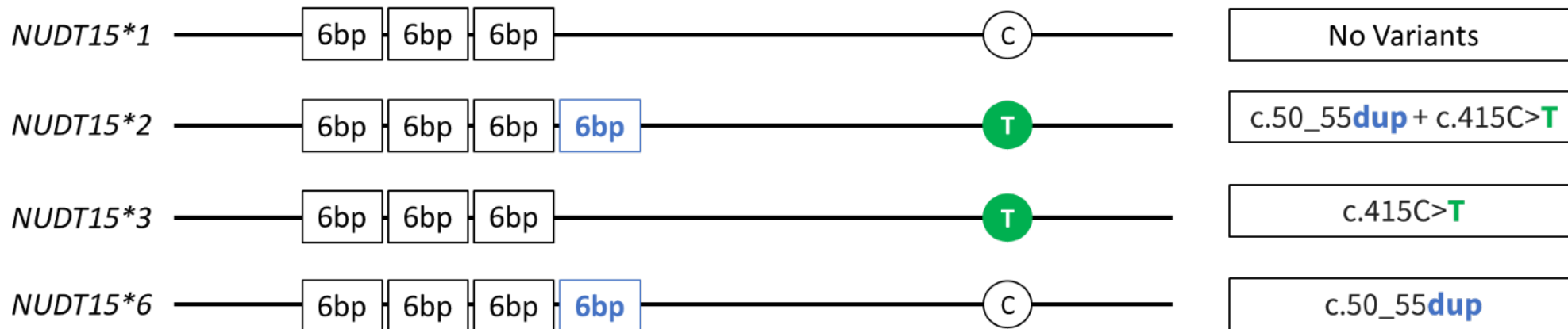
Alert Action:

- Cancel Order
- Override Alert
- Modify Order Dose

OK

Oncology PGx challenges

- Rare variants not called
 - Among 113 patients with WES, found 2 exonic *TPMT* variants, p.E98* (rs72552739) and p.Thr113= (rs17839843)
- Phasing with short reads not possible
 - The *NUDT15* result cannot be fully distinguished between *1/*2 (IM) and *3/*6 (PM). Genotyping the patient's biological parents could aid in assessing the true metabolizer status.



Oncology PGx challenges cont.



- Coverage of some pharmacogenes on WES is poor
 - Upcoming switch to long read sequencing



- Clinical Decision Support
 - Ordering of mercaptopurine place holder
 - First gene-drug pair to be implemented so lots of learning



- Ordering add-on test
 - Genetics lab intercepts orders for send out *TPMT* testing and encourages replacement with sequencing test for both genes



- Turn around time ~45 days



KidDose panel test

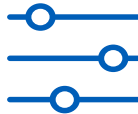
- Performed on QuantStudio™ 12K Flex instrument with 384-well format
- Custom-designed TaqMan™ panel including modifications to existing PGxExpress content:
 - Added *CYP2D6*, *CYP2C9*, *TPMT*, *NUDT15*, *SLCO1B1* variants and *CYP2D6* copy number (5'UTR, Exon 9)
 - Removed *CYP1A2*, *ABCB1*, *ADRA2A*, *F2*, *F5*, *MTHFR*
- Panel approach and workflow is designed to cover AMP Tier 1 & 2 alleles, be low-cost and competitive with external offerings, and a TAT of 10 days or less
- Validation process is underway



Panel test challenges



- There are no TaqMan[®] assays for some variants of interest (*CYP2D6*21, CYP3A4*20*)



- Most common haplotype assumed – not able to be phased



- You can't see what you don't test for



- Lack of support in training on instrument & software



PGx from long read whole genome sequencing

Advantages

- Phasing of haplotypes
 - no more *NUDT15**1/*2 or *3/*6
- Calling alleles with variants in non-coding regions
 - *CYP2C19*, *CYP3A5*
- Accurate *CYP2D6* hybrid allele calls
- Others have done it
- Discovery of novel alleles

Disadvantages

- New analysis pipeline to develop and validate
- What to do with novel alleles?
- Longer turn around time for results than panel test
- Lots of data

Clinical lab

JD Nolen
Carol Saunders
Midhat Farooqi
Lisa Lansdon
Joe Alaimo
Melanie Patterson
Byunggil Yoo
Jeff Johnston
Lee Zellmer

Clinical champions

Clinical Pharmacology & GOLDILOKs

Jon Wagner
Tracy Sandritter
Alexa Pagano
Sarah Suppes
Anne Eveland
Casey Weston
Erin Boone
Wendy Wang
Stephani Stancil
Andrea Gaedigk
Jen Goldman
Steve Leeder

Health Informatics

Ryan McDonough
Kate Vanlandingham
Kirstin Peterson
Katie Burt
Josh Herigon
Darrell Hall

Research Informatics

Mark Hoffman
Kevin Power

