Advances in Genomics of Monogenic Diseases: From Diagnostics to Therapeutics

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NephKids 2025

Chennai

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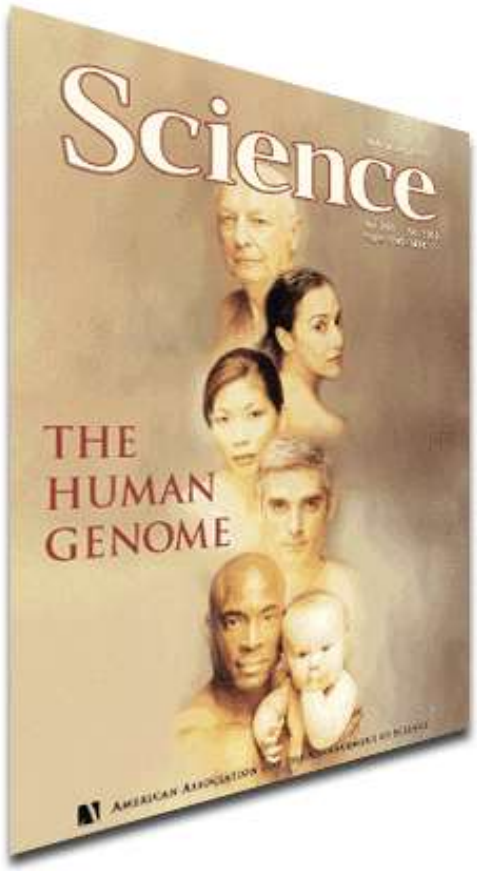
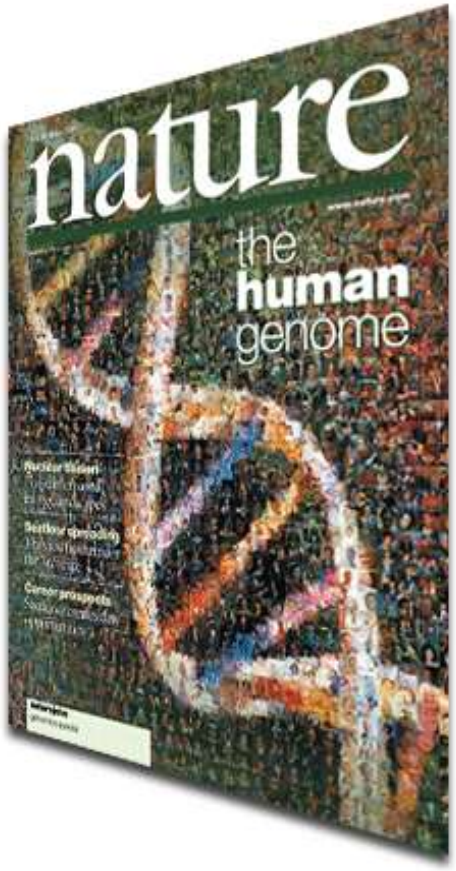
OUTLINE

- Foundational events making genomic tests accessible and useful
- Genomics of kidney diseases and utility of genomic testing
- Leveraging genomics testing for therapeutics
- Challenges with integrating genomic testing in clinical workflow

Mapping of Human Genome





3 billions base pairs (ATGC)

99.6% inter-individual identity (yet 4 millions differences)

Genes [20,000-25000; 8000 mapped to Mendelian diseases]
Sequences < 5 % - Exons - 1.5 % [Coding] Introns – 3.5 % [Non-coding]
95 % disease causing variants identified in exonic regions

Nucleic Acids Res 47: D1038–D1043, 2019

INNOVATION > HEALTHCARE

The First Child Saved By DNA Sequenci

By Matthew Herper, Former Staff. I cover science and medicine, and believe this is biology's century.

Published Jan 05, 2011, 04:57pm EST, Updated Aug 11, 2011, 12:19pm EDT

GENETICS

For the First Time, DNA Sequencing Technology Saves A Child's Life

The future of medicine has arrived.

Posted January 10, 2011

Costed around 70,000 USD for exome sequencing

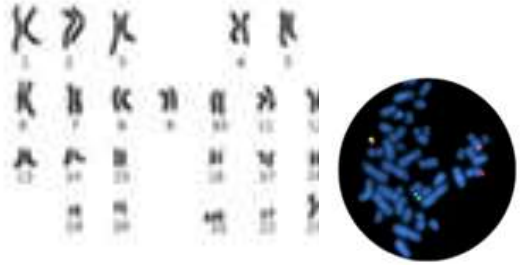
The hurdles to getting DNA sequencing from the laboratory to the hospital are huge.

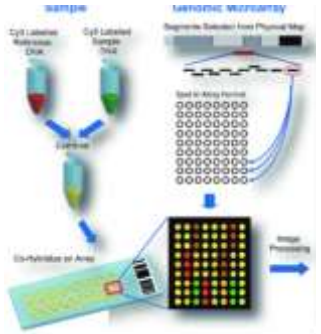
Types of genetic (genomic) testing methods

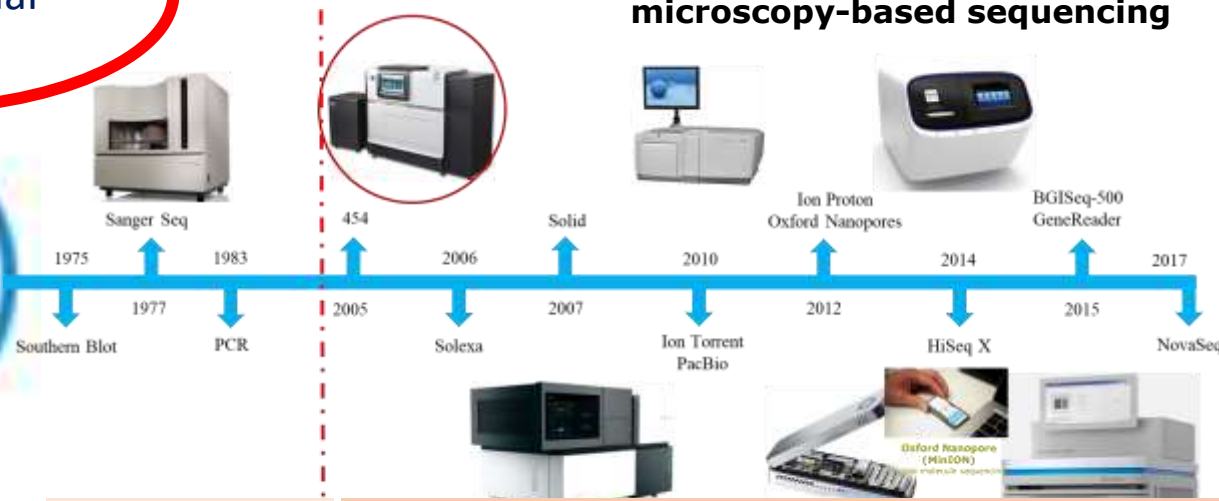
Chromosomal anomalies

Copy Number Variants

Single nucleotide variants/Smal InDels







Karyotyping

FISH

Microarray (CGH)

- Multiplex ligation dependent probe amplification (MLPA)

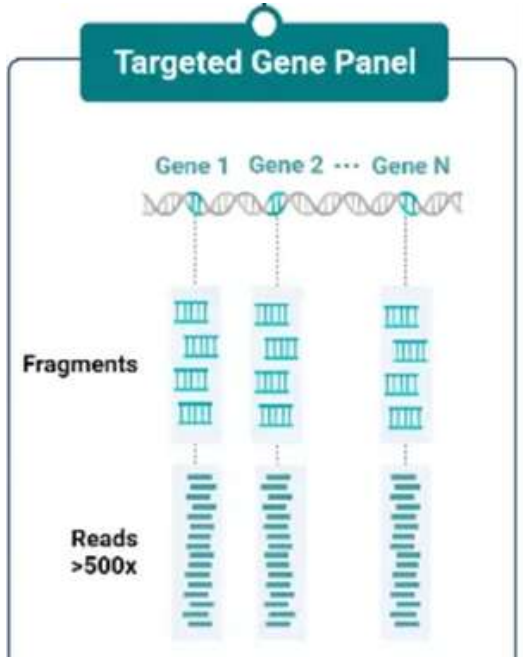
Sequencing

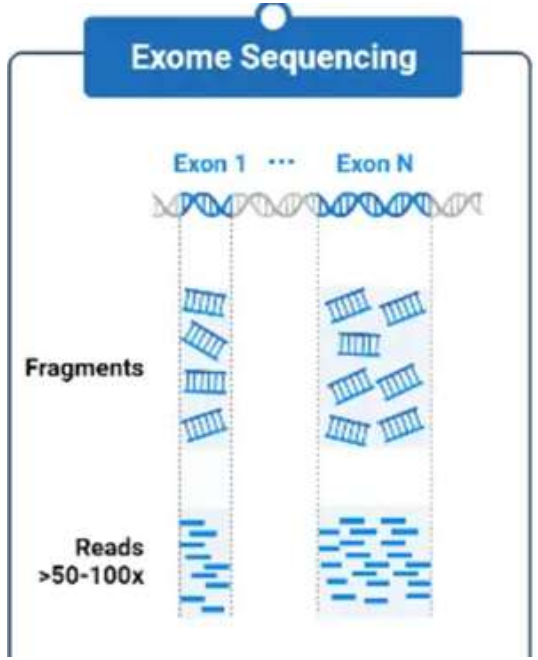
Sanger Sequencing

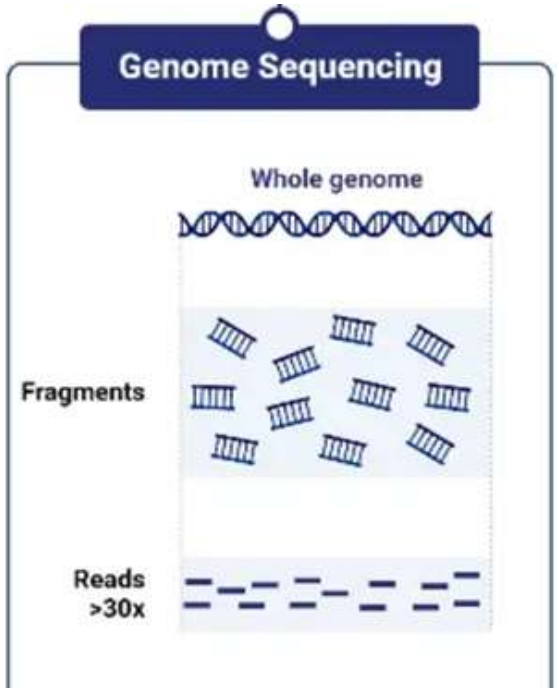
Massively Parallel Sequencing (Formerly called Next Generation Sequencing)

- Exome Sequencing
  - Targeted Panel
  - Clinical exome (CES)
  - Whole exome analysis (WES)
- Whole genome analysis (WGS)

Choosing a genomic testing method



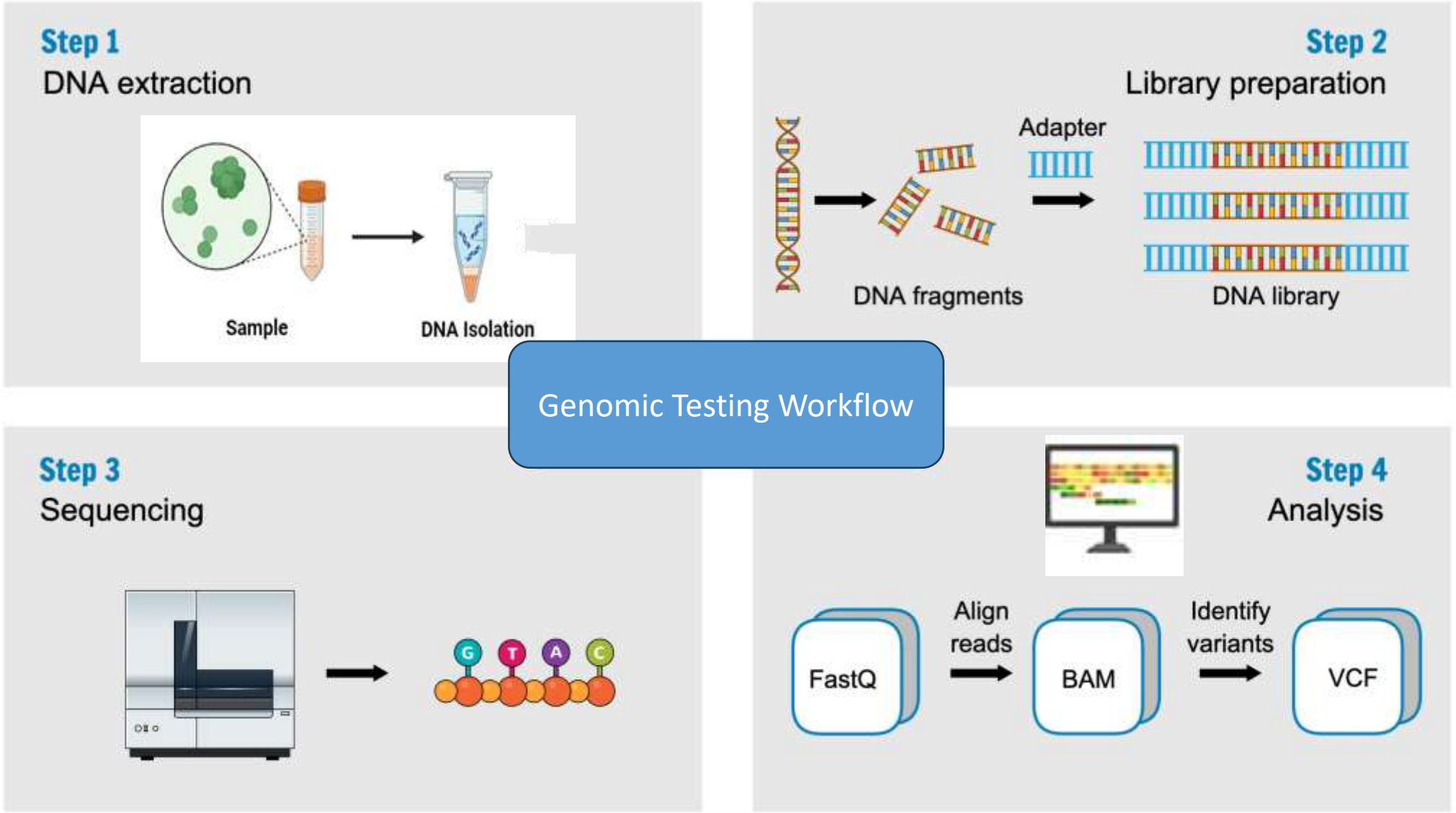




Coverage	All exons of selected genes (10-500)	Exons of all genes in OMIM (~8000) Exons of all genes known (~25000)	All genes and noncoding DNA
Accuracy	High	Good	Low to Good
Time (TAT)	Quick (2-4 weeks)	Long (2-6 weeks)	Longest
Cost	Most cost effective	Cost effective	Most expensive
Utility	Disease phenotype/clinical diagnosis certain	Phenotype overlap/heterogeneity; Unknown clinical diagnosis; CNVs	Phenotype suggestive of genetic cause and exome sequencing is negative

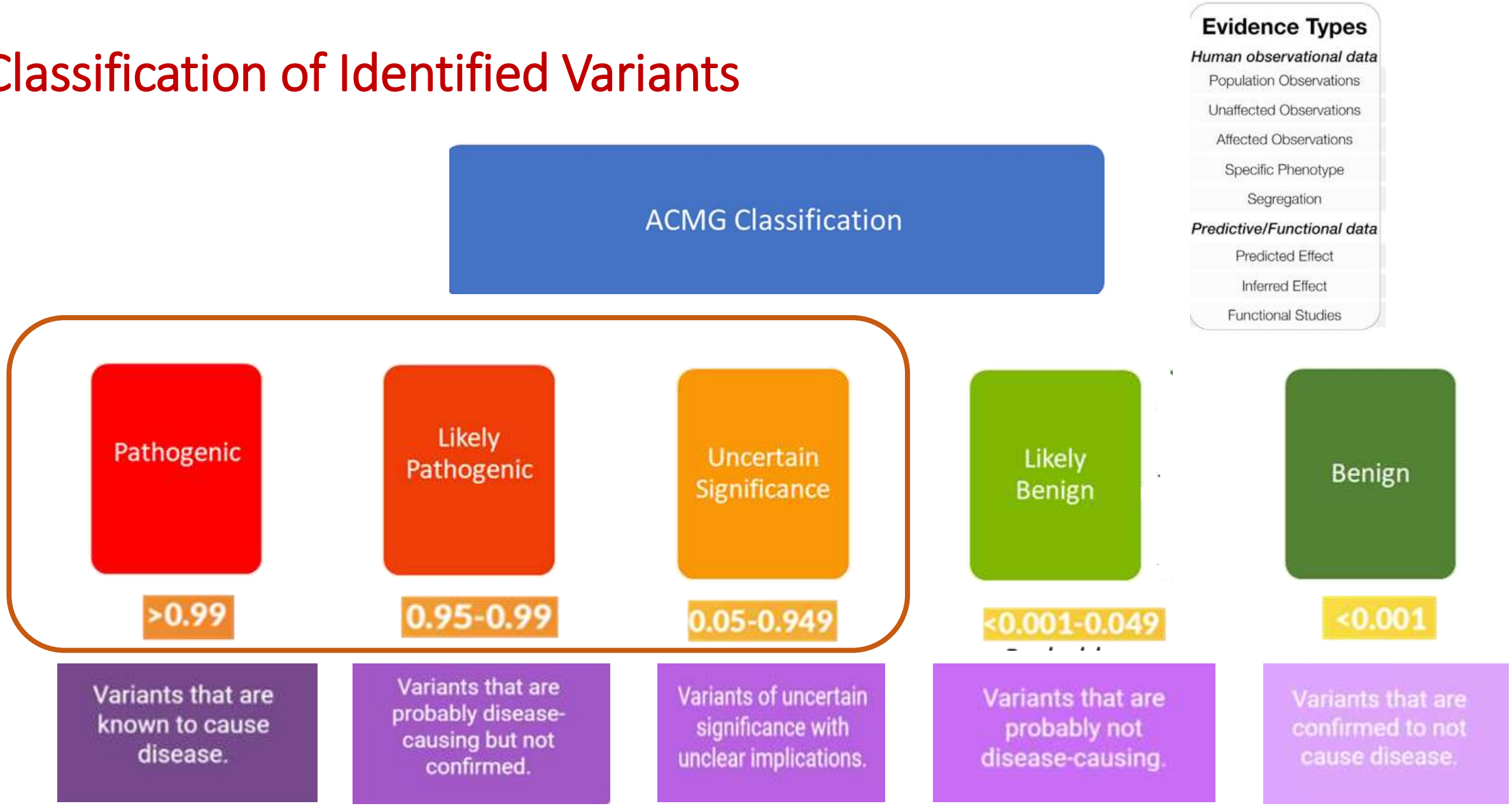
https://biologynotesonline.com/

General workflow of clinical genomic sequencing tests

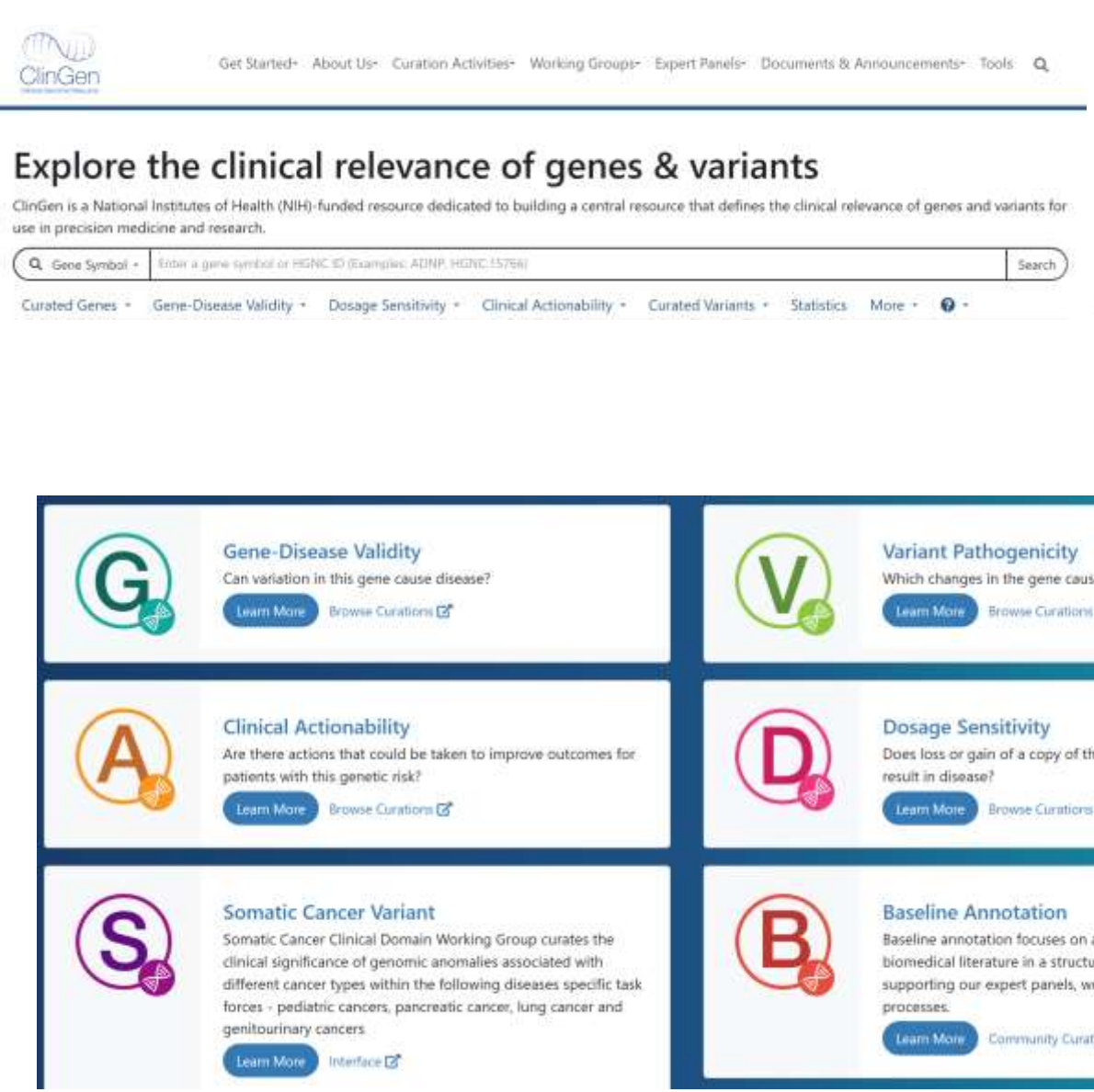


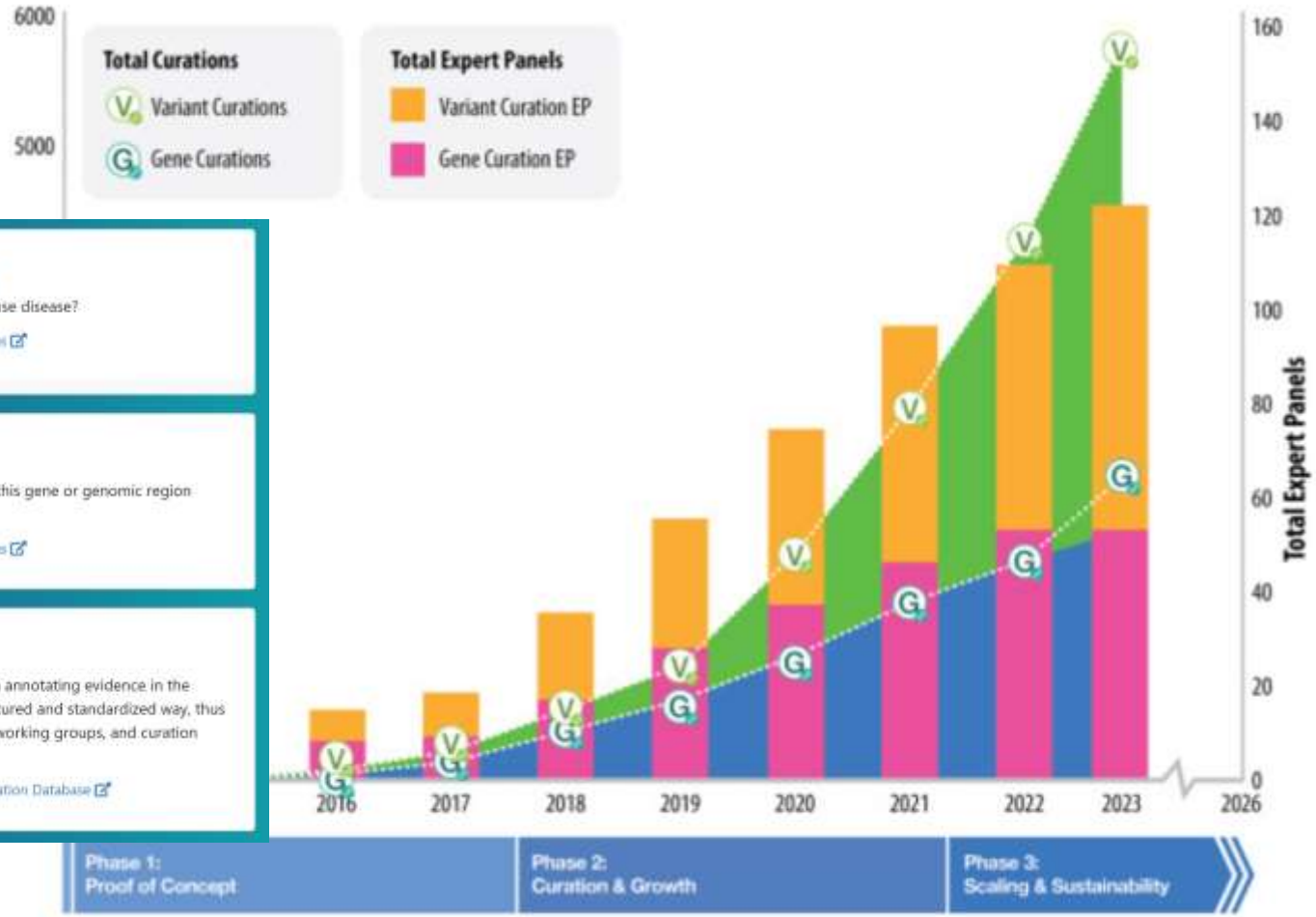
https://mindthegraph.com/

Classification of Identified Variants



Genet. Med. 17, 405–24 (2015)



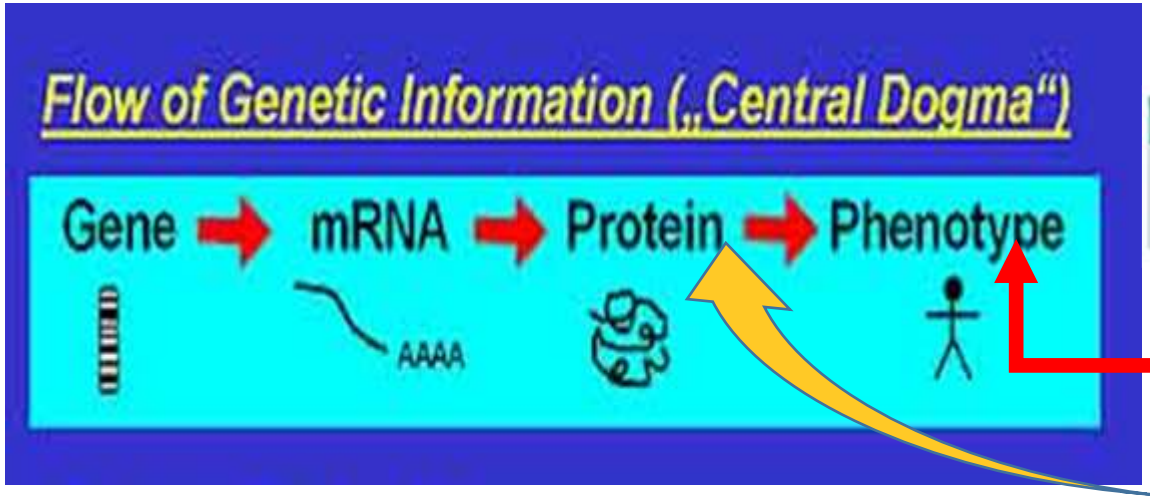


Bayesian Points Classification for variant classification

[Expert Panels - ClinGen | Clinical Genome Resource]

Interpretation of Genomic Test Report

Variants identified must be evaluated for causation



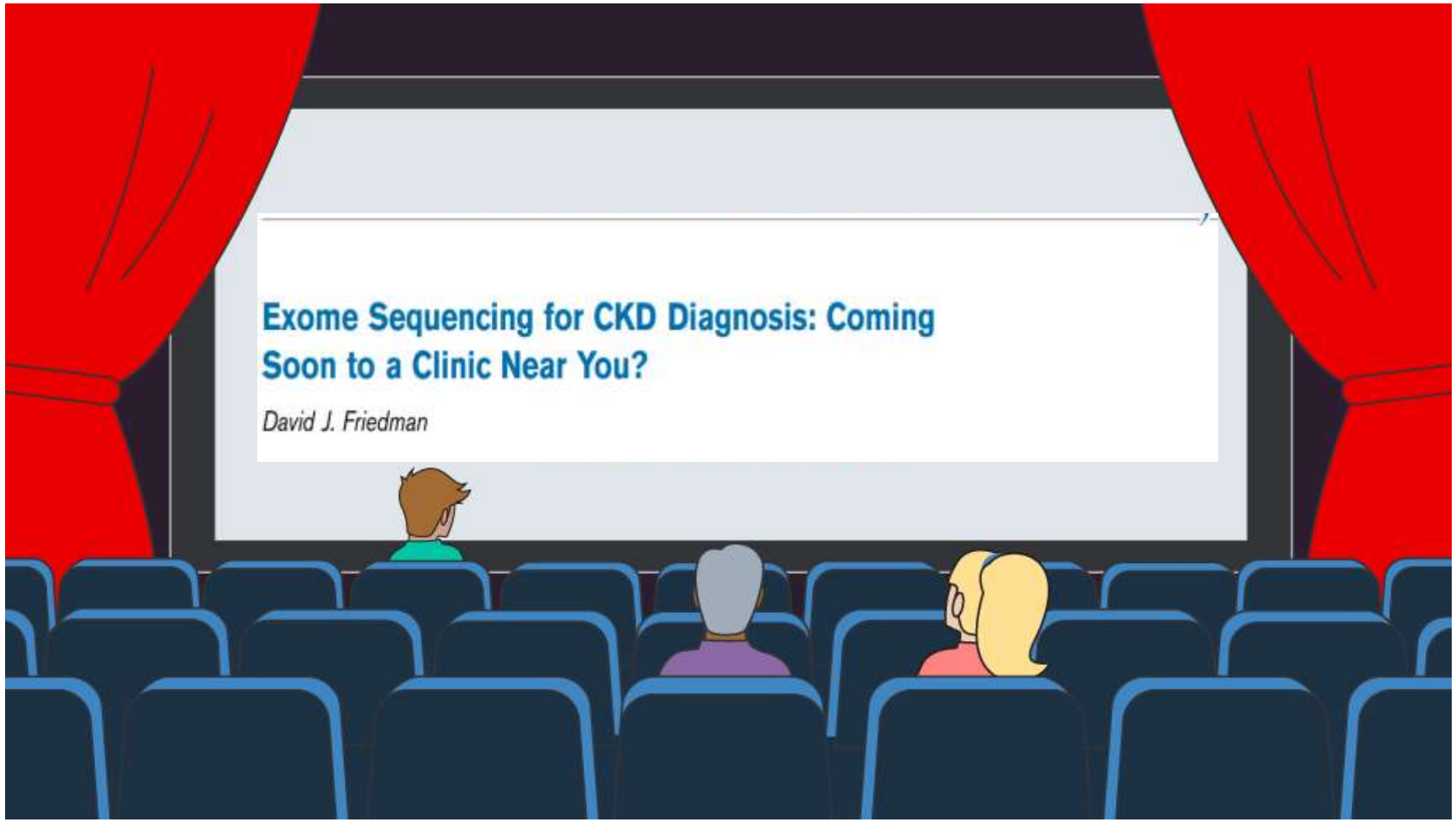
Gene (Transcript) #	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
***WT1* (-)** (ENST00000332351.3)	Intron 9	c.1432+4C>T **(5' splice site proximal)**	Heterozygous	Nephrotic syndrome type-4	Autosomal dominant	Likely Pathogenic

Disease	Kidney Phenotype	Extra kidney features
Frasier Syndrome	Nephrotic syndrome	Ambiguous genitalia, gonadal dysgenesis with risk of gonadoblastoma

Variant level assessment and interpretation

Case level interpretation

Case level interpretation incorporates both pathogenicity of variants and how well the variant matches the phenotype



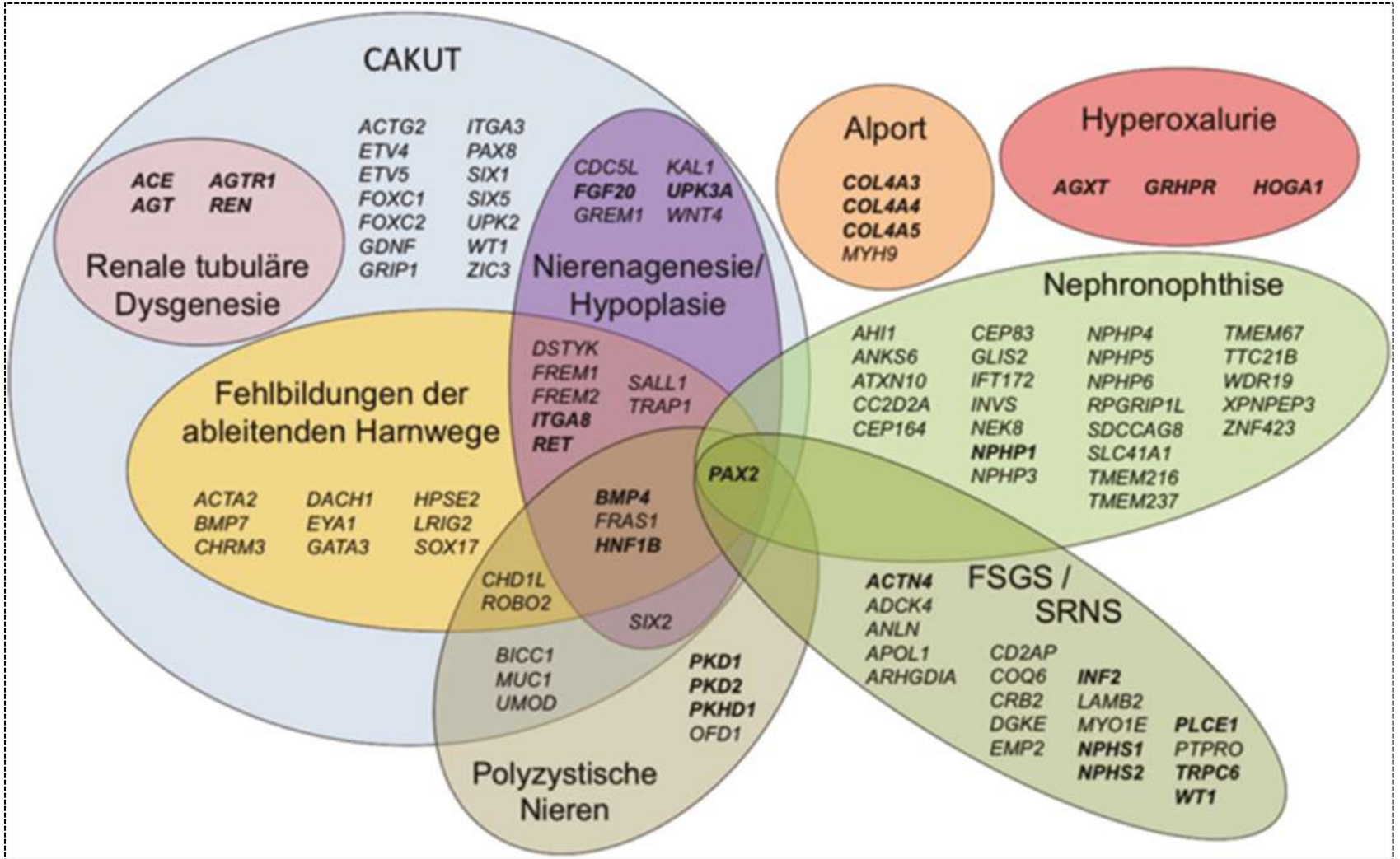
American Journal of Kidney Diseases, 2018; 72 : 761-763

Monogenic Kidney Diseases

- **625 Mendelian disorders associated with kidney and urological traits**

Over 70% of CKD cases under the age of 25 years can be attributed to a genetic etiology

> 500 genes associated with kidney diseases



Kidney Int 2020; 98, 590–600
Kidney Int. 2016; 89: 468–475

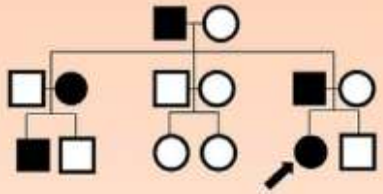
Patient characteristics that increase the diagnostic yield of genetic testing

Young age of onset

Examples:

- Nephrotic syndrome
- Microscopic hematuria
- CKD
- HTN/electrolyte abnormalities

Strong family history



Examples:

- ADPKD
- Alport syndrome
- Young onset of ESKD

Cystic/anatomic abnormalities

Examples:

- Multiple renal/hepatic cysts
- CAKUT

CKD of unclear etiology

Examples:

- No diagnosis despite thorough work up
- Tubulointerstitial disease of unclear cause (ADTKD)

Extrarenal manifestations

Examples:

- Liver cysts
- Developmental delay
- Skeletal abnormalities
- Vision/hearing loss

Am J Kidney Dis. 2024; 84(5):632-645

Varying yield using molecular genetic analysis and genetic heterogeneity

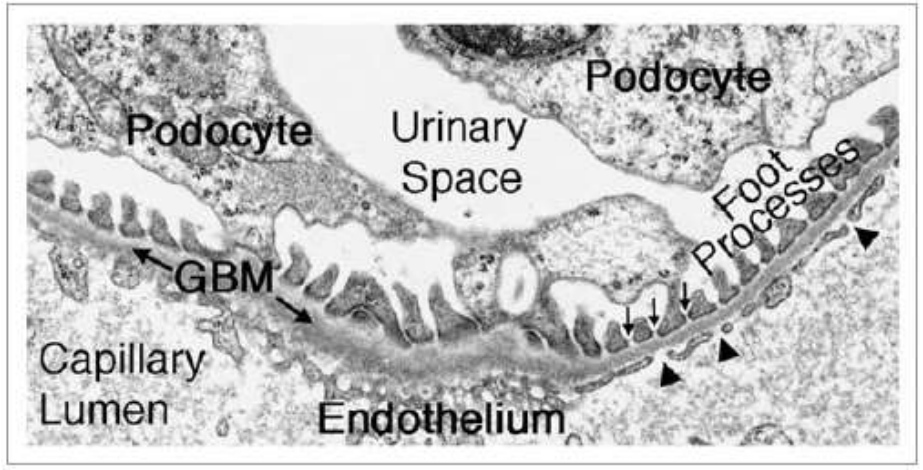
Glomerular	25 - 80 %
Tubular Diseases	30 -90 %
Nephrolithiasis	10 - 60 %
Cystic Diseases	20 - 80 %
Ciliopathies	
CAKUT	5 - 22 %

- Genotypic heterogeneity
- Phenocopy
- Pleiotropy

Nephrol Dial Transplant (2020) 35: 390–397

CKD is characterized by significant phenotypic heterogeneity and expanded phenotype

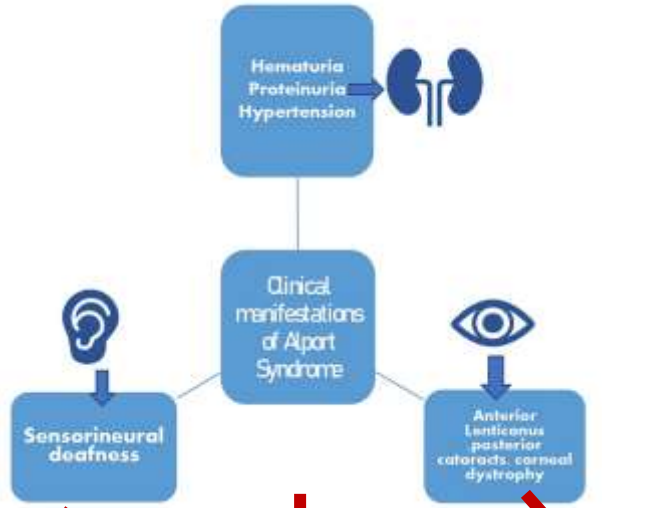
Podocytopathies



Nephrotic Syndrome

Proteinuria

Chronic Kidney Disease



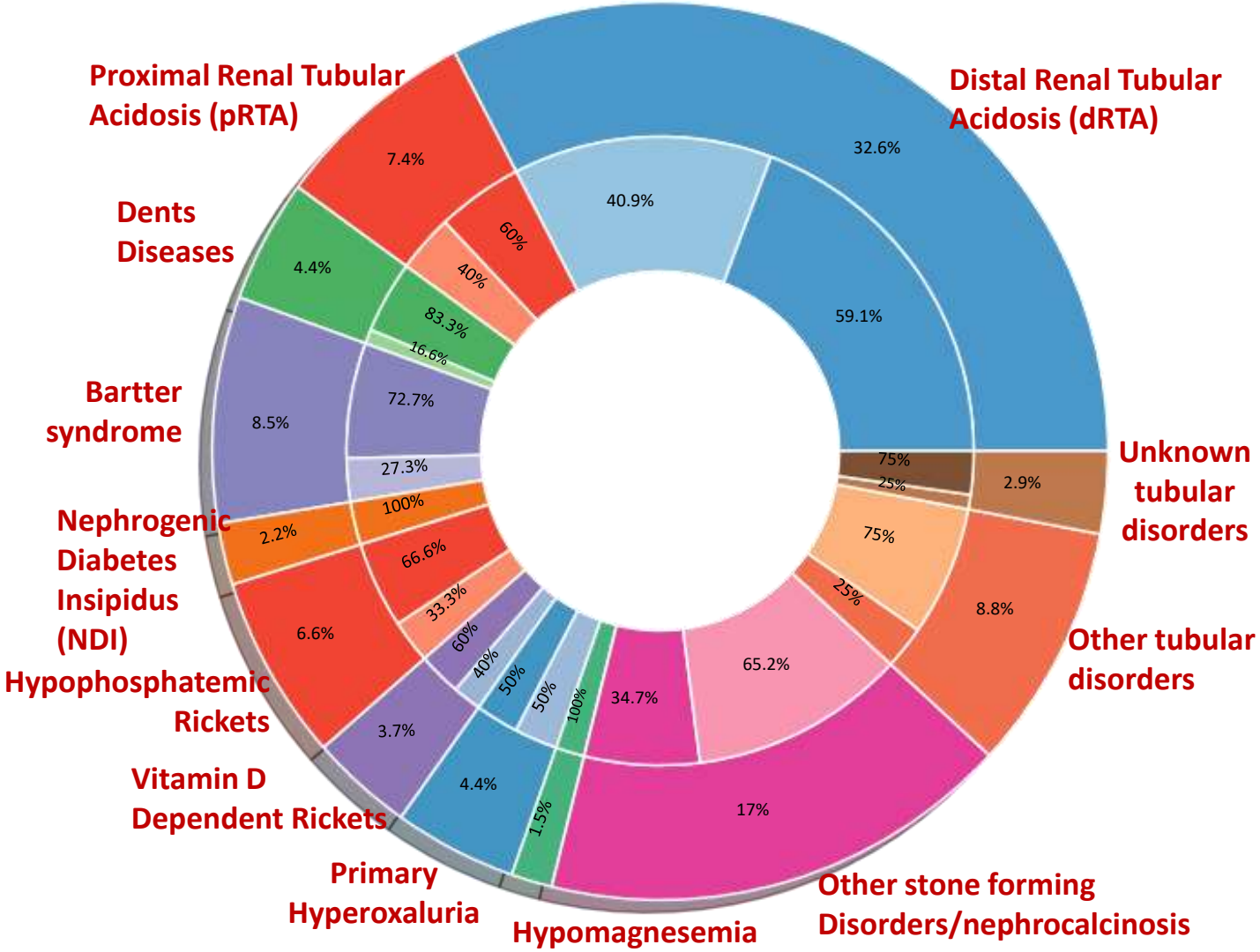
nephrotic with FSGS lesions

Familial IgAN

Cystic phenotype

Nephrol Dial Transplant (2020) 35: 390–397
Am J Kidney Dis.2021 ;78(6):857-864

Genetic testing in Children with tubular disorders: (n = 135/225)



Deciphering the mutation spectrum in south Indian children with congenital anomalies of the kidney and urinary tract

Ambili Narikot[1], Varsha Chhotusing Pardeshi[1], A. M. Shubha[2], Arpana Iyengar[3] and Anil Vasudevan[1,3*]

Total number of subjects recruited till date
128

Subjects excluded from the study
18

Subjects screened with complete data
110

Subjects included for Genetic screening
69

Clinical data collected: Socio-demographic data, Antenatal History, Birth and Anthropometric details, Investigations and Renal Imaging reports were collected.

Blood sample: 4ml was collected in EDTA tubes and DNA was extracted

Designing of Customized CAKUT gene Panel:

- Exonic regions of 31 genes
- 98.99% Coverage

Patient Characteristic		Genotyped Cohort (n=69)
Age (yrs.) (median;IQR)		6 (4.5-9)
Gender (Male: Female)		56: 13
Renal phenotype	Vesico-Ureteric Reflux (VUR) (Bilateral: Unilateral)	23(14:9, 33.33%) 10 (14.49%)
	a. VUR with Hypodysplasia	13 (18.84%)
	b. VUR without Hypodysplasia	
	Hypodysplastic kidney	0
	Posterior Urethral Valve (PUV)	27 (39.13%)
	Duplex Collecting System	3 (4.34%)
	Multi-Cystic Dysplastic Kidney (MCDK)	5 (7.24%)
	Ureteropelvic Junction Obstruction (UPJO) (Bilateral: Unilateral)	5 (1:4, 4.54%)
	Vesicoureteral Junction Obstruction (VUJO) (Bilateral: Unilateral)	2(0:2, 1.81%)
	Renal Agenesis	3 (4.34%)
	Horseshoe Kidney	1(0.9%)
	Ectopic kidney	0
Family history[a]		0
Consanguinity[a]		15 (21.73%)
Syndromic		3 (4.34%)
No of subjects with CKD (≥ stage 2) @ recruitment		9 (13.04%)

ACMG Classification (65)

Likely Pathogenic/Pathogenic
0

Variant of unknown significance
39 (60%)
25.6% (10/39)- Potential damaging

Likely Benign
26 (41.3%)

BMC Nephrology (2022) 23:1

Integrating genomic assessment into clinical workflows

Confirmation of diagnosis/Help make a diagnosis
Examples

Alport syndrome

Monogenic SRNS

CKD of unknown etiology

Conditions amenable to specific screening for extrarenal manifestations

Examples:
- HNF1B: diabetes/Hypomagnesmia
- WT-1
- Fraiser syndrome – Gonadal dysgenesis

Conditions amenable to specific disease modifying therapies
- Co010 genes (SRNS)
- CTNS (cystinosis)
- Tubulopathies

to nonspecific renoprotective strategies
Example
- COL4A34/5 (Alport) and RAAS blockade

Avoidance of prolonged Immunosuppressive therapies

Example
- Glomerular disease due to mutations in Alport genes (COL4A345

Conditions at risk for recurrence after kidney transplantation
Examples
- (CFH/CFIC3): aHUS
- (AGXT, GRHPR, HOGA): primary hyperoxaluria (PH)
- Genetic causes of SRNS have low recurrence rate
- **Donor selection**

Conditions for which genetic testing is relevant for reproductive counseling

Example:
•Prenatal/ preimplantation diagnosis

Expanding role of genetic testing as part of clinical management of patients with kidney diseases

Developing a genetic testing panel for evaluation of morbidities in kidney transplant recipients

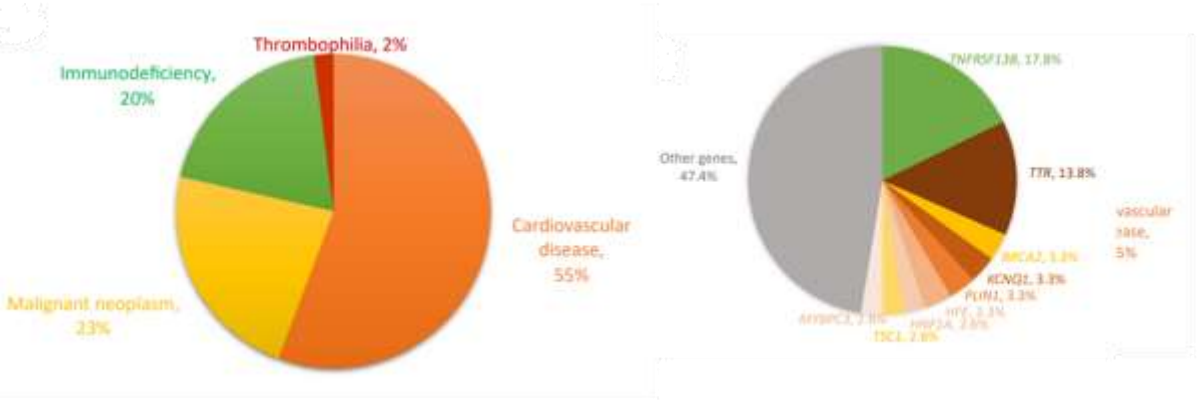
Check for updates

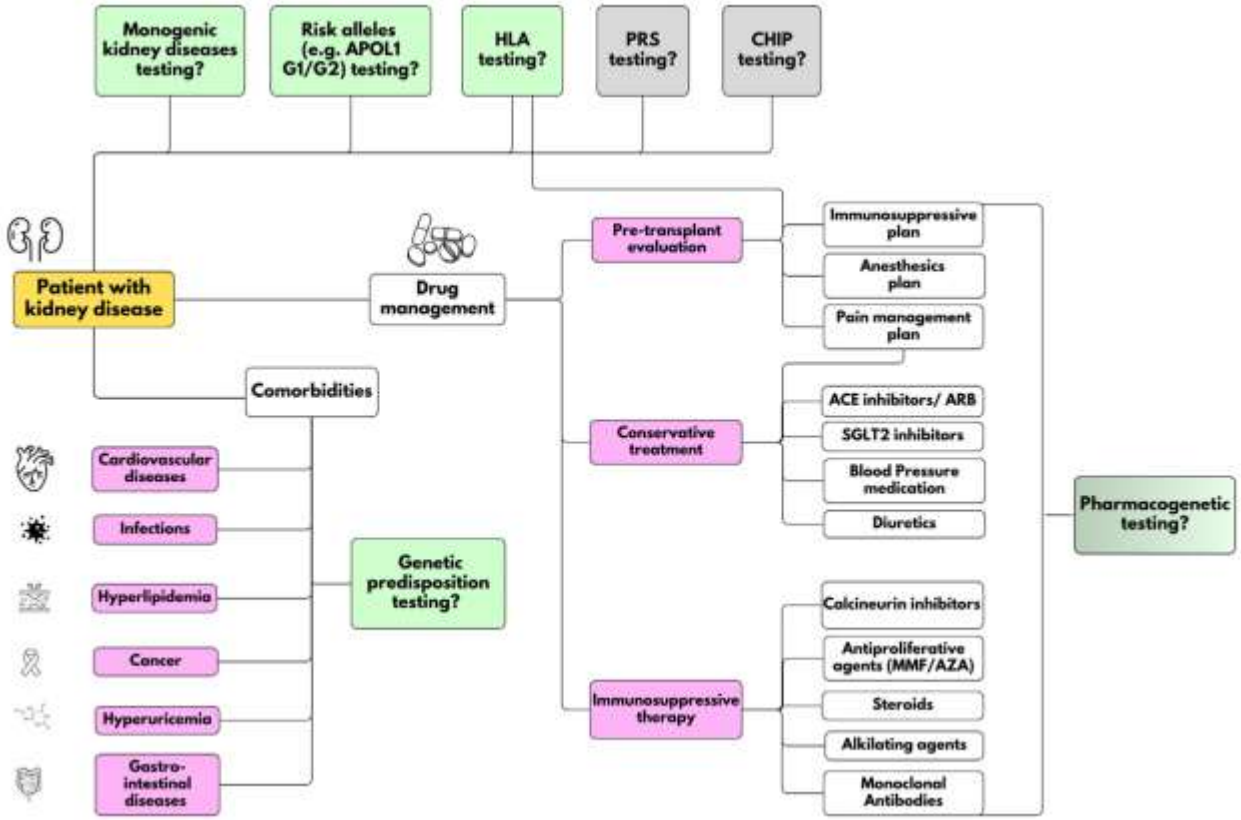
see commentary on page 18

OPEN

Becky M. Ma[1,2,3], Naama Elefant[1,2], Martina Tedesco[1,2,4], Kelsie Bogyo[1,2], Natalie Vena[1,2], Sarath K. Murthy[1,2], Shiraz A. Bheda[1,2], Sandy Yang[1,2], Nikita Tomar[1,2], Jun Y. Zhang[1,2],

Transplant morbidity panel (355 genes) associated with major post-transplant complications including cardiometabolic disorders, immunodeficiency, malignancy, and thrombophilia





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Role of Genomic Testing in Diagnosis and Management of kidney Disease

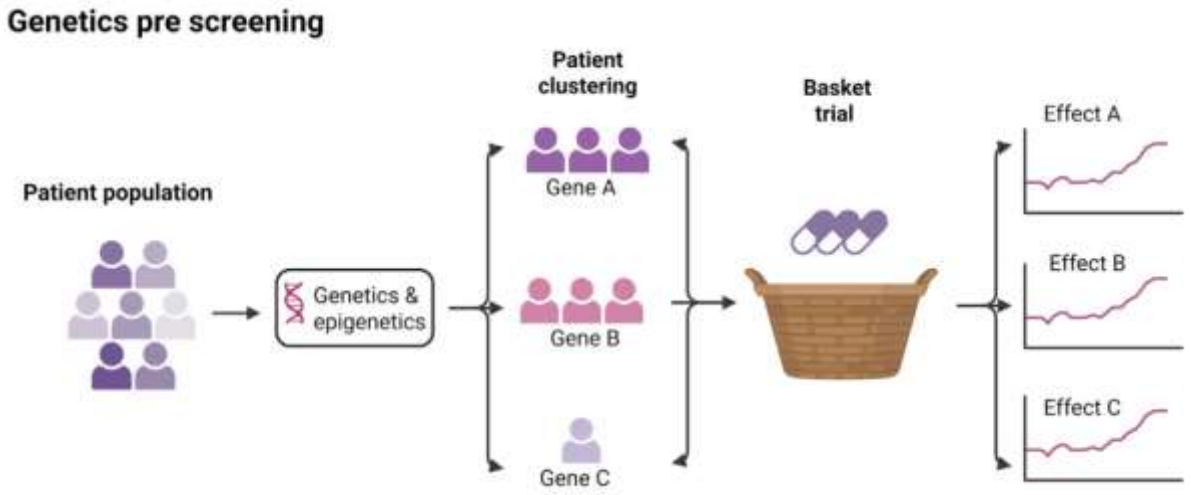
From optional to essential

Use at the beginning of a diagnostic workup rather than the end

From Womb to Tomb

Treatment of Monogenic Diseases

- Supportive therapy
- Biological molecules
- New drugs
- Drug repurposing
- Gene modifications – knockout/gene therapy



Classes of Genetic Kidney Disease and Existing Therapies

Genetic Kidney Disease Subgroup	Exemplar Conditions	Treatment			Therapeutic Interventions
		Supportive	Modifiable	Curative	
CAKUT		•	•		Surgery
Glomerular	Alport syndrome	•	•		ACEi/ARB
	COQ10 deficiency				COQ10- supplementation
Cilial	NPHP related ciliopathies	•			
Cystic	ADPKD	•	•		ACEi/ARB; Tolvaptan for ADPKD
ADTKD	UMOD	•	•		ACEi/Allopurinol/Febuxostat
Tubular	Bartter Syndrome	•	•		NSAIDs and Electrolyte replacement
	Gittelman Syndrome				Electrolyte replacement
	Gordon syndrome				Thiazide diuretic
	Nephrogenic diabetes insipidus				Thiazide diuretic and NSAIDs
	Cystinuria				Penicillamine
Metabolic	Fabry Disease	•	•		Enzyme replacement
	Primary hyperoxaluria		•		RNAi
	Cystinosis		•		Cysteamine
Complement mediated	Atypical HUS		•		Eculizumab
			•		Ravalizumab
			•		C5 inhibitors

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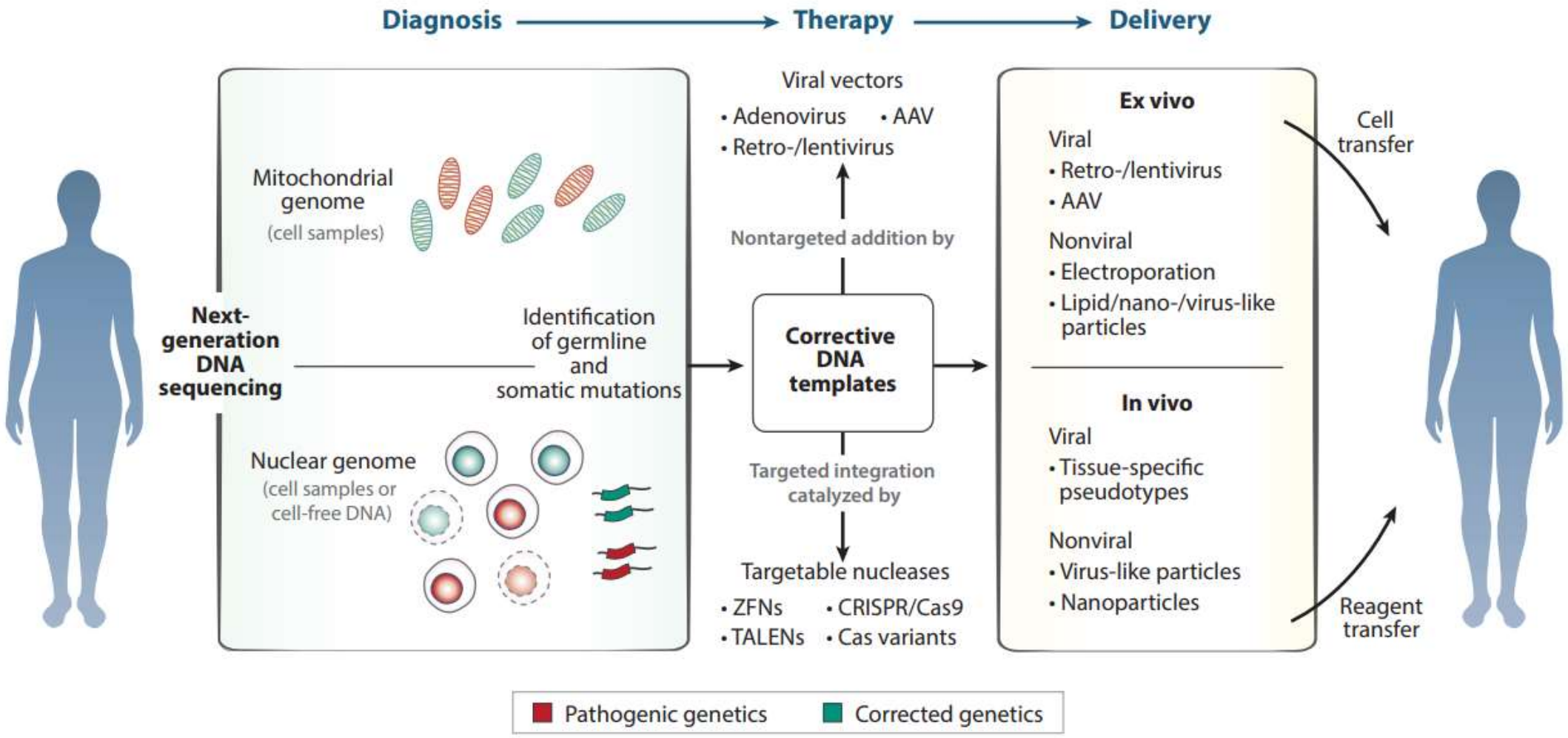
Modes of Genetic Therapy

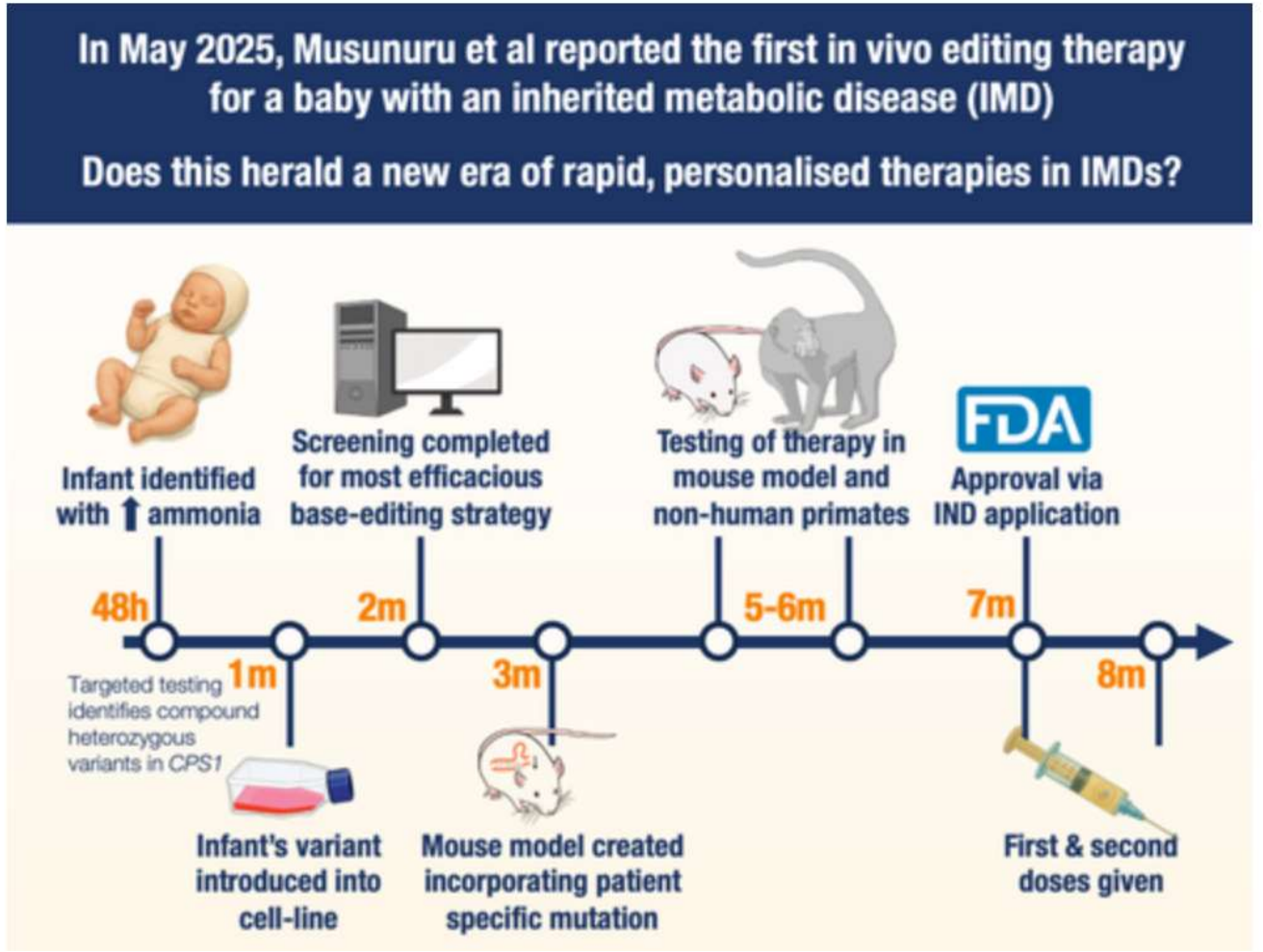


Annu. Rev. Pathol.Mech. Dis. 2021. 16:145–66

Gene therapy

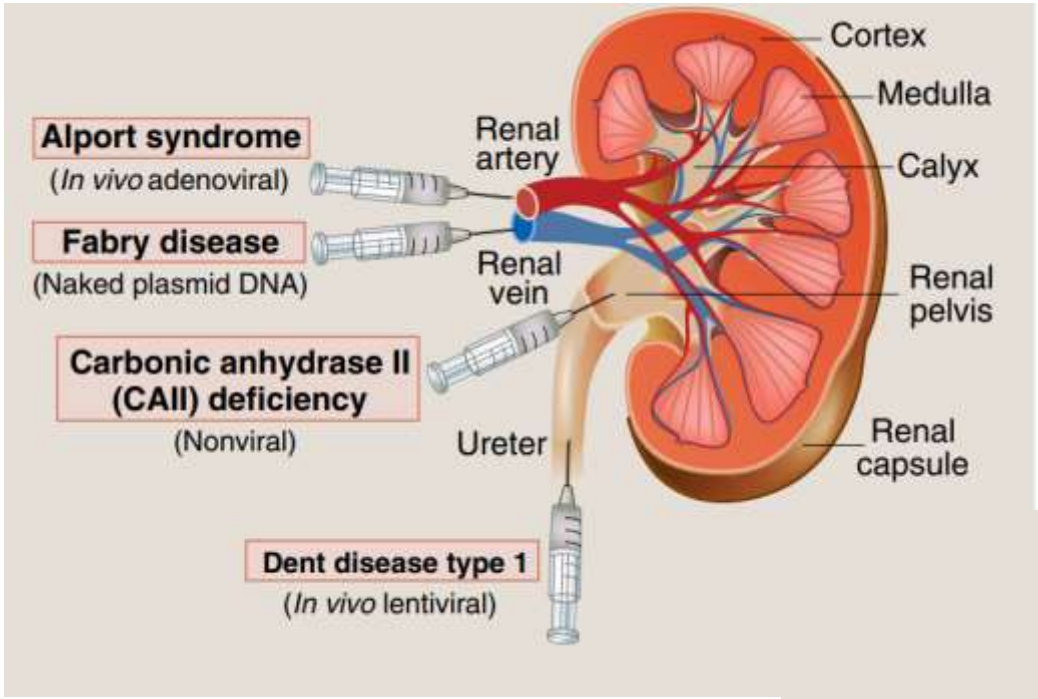
N-of-1 Trials

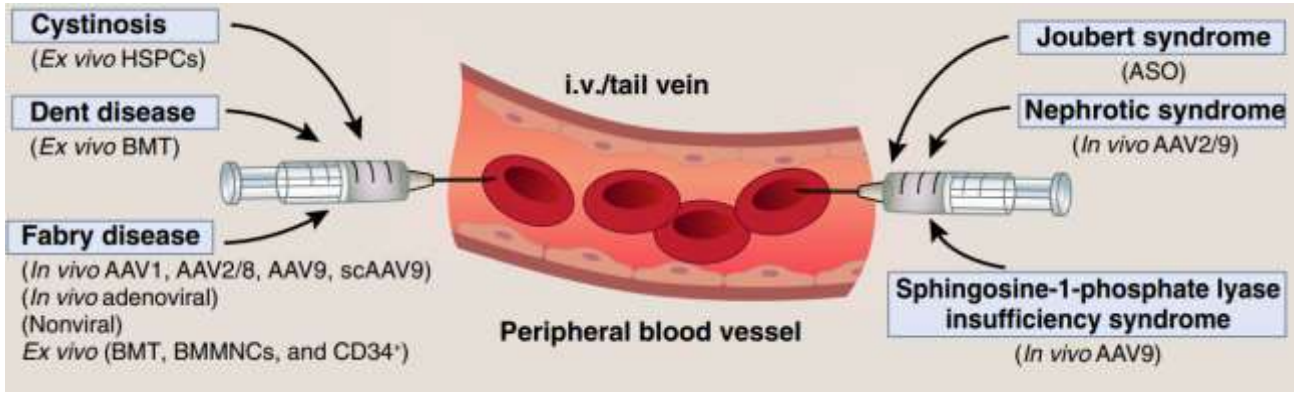
First in vivo gene editing therapy for a baby with an inherited metabolic disease (IMD)

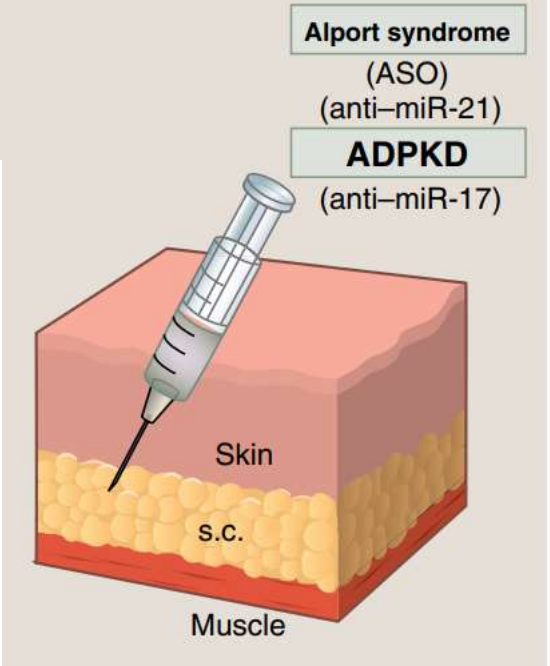


N Engl J Med 2025;392:2235-43; Inherit Metab Dis. 2025 Jul;48(4):e70056

Targeted gene therapy for genetic kidney diseases





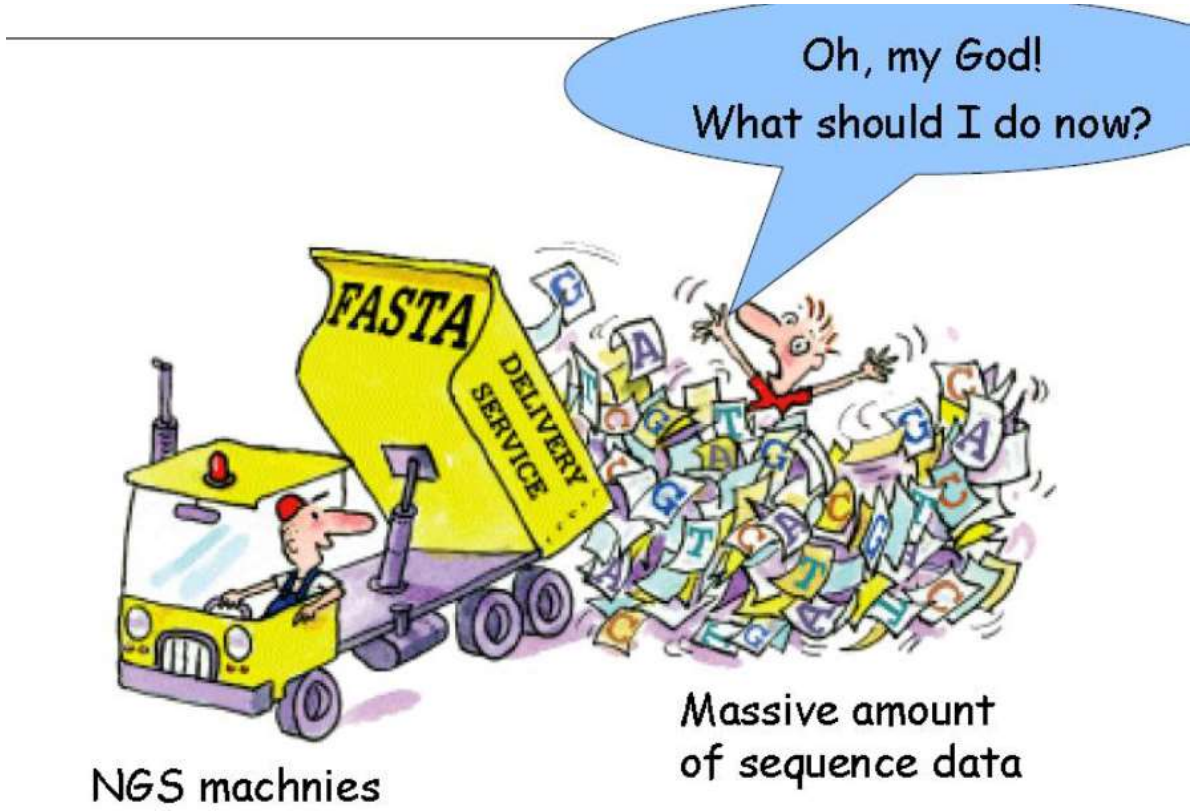


Kidney International (2024) 106, 1051–1061

Limitations and Challenges

Single gene sequencing:
SANGER sequencing

Multiple gene sequencing:
NGS= Next generation sequencing



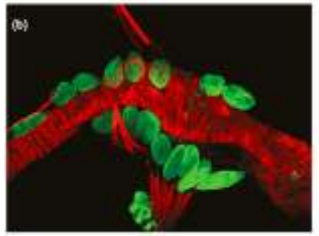
Technical Challenges

- Gene_Disease relatioships
- Prioritization and interpretation of variants
- Incidental/Secondary findings

Practical challenges

- Medical, Social and ethical challenges
- Cost of testing
- LACK of Therapy

Variants of Unknown Significance



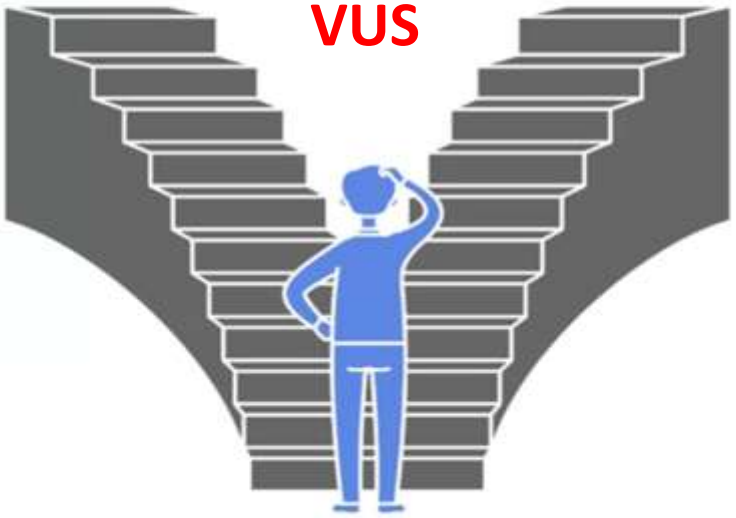
Criteria Not Met

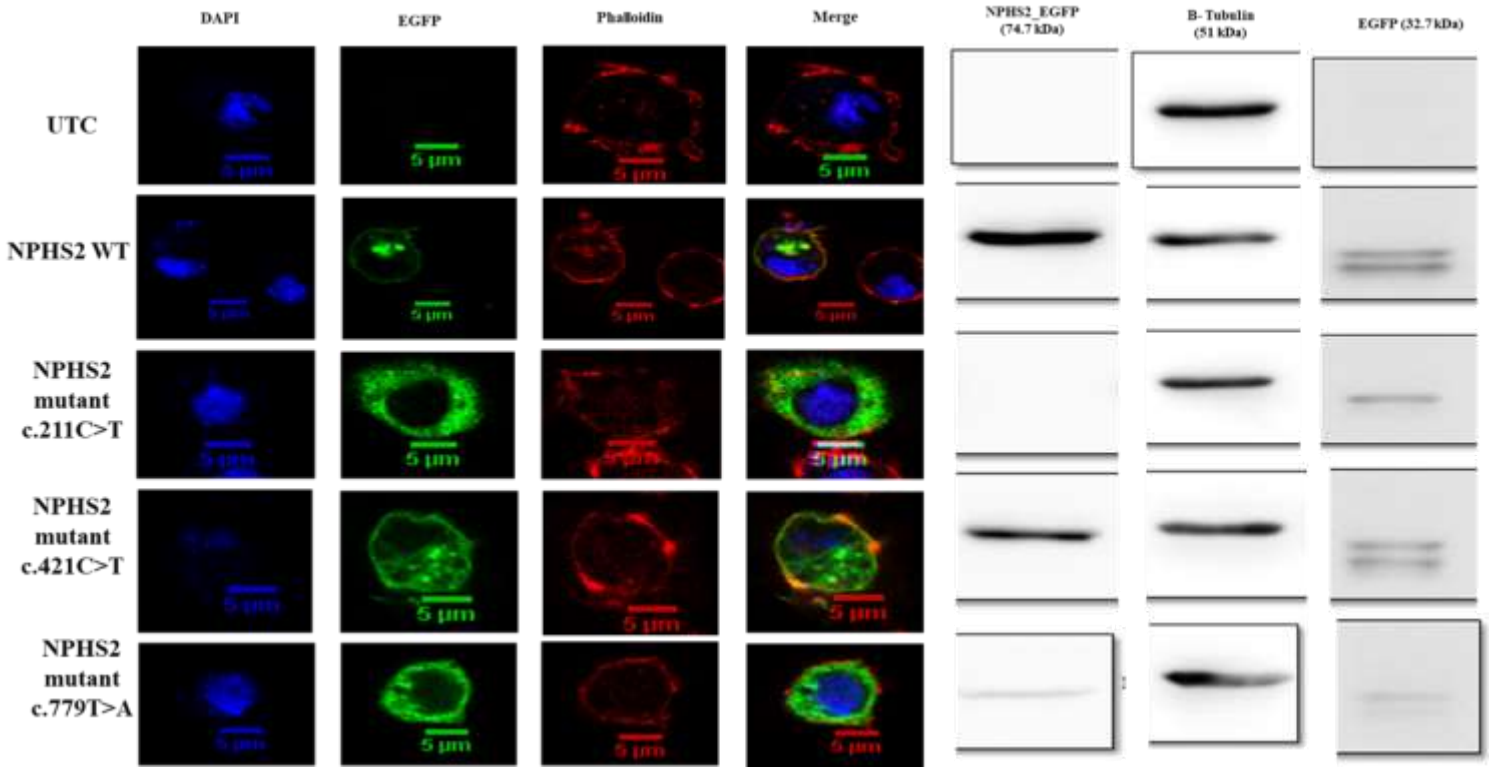
The variant is classified as VUS because other criteria are not satisfied.

Contradictory Criteria

The variant is classified as VUS due to contradictory benign and pathogenic criteria.

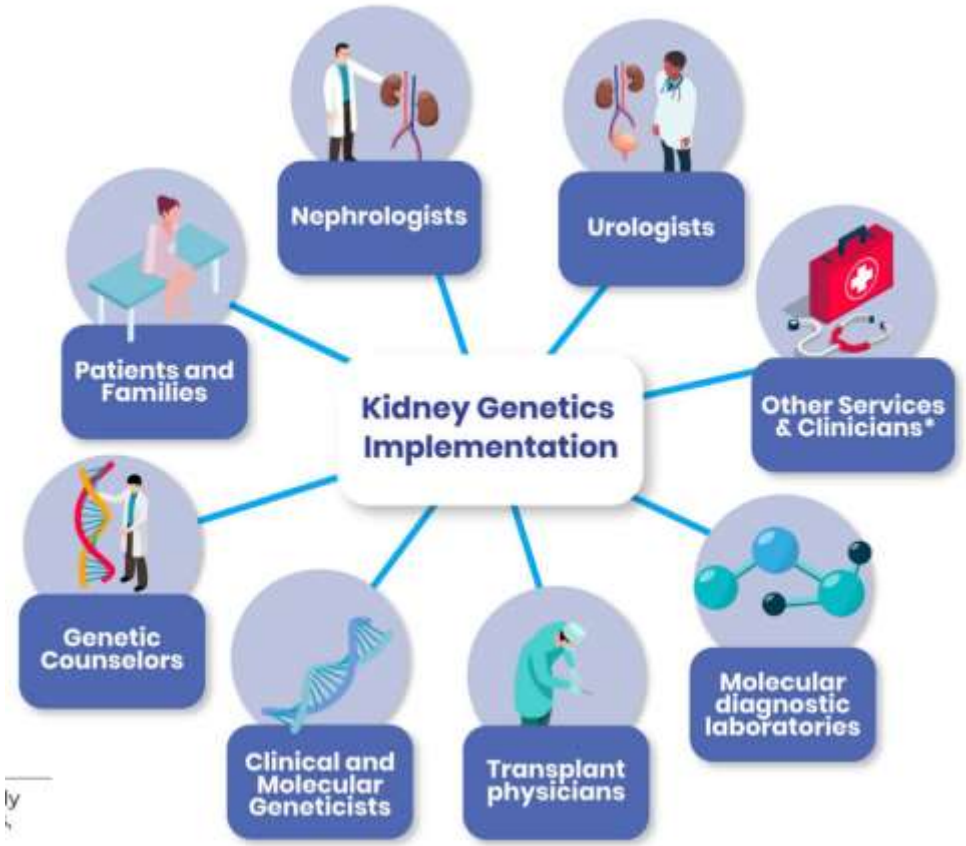
VUS





Model of care for implementation of genetic testing

Multidisciplinary genetic clinic or Nephrogenetic clinic



Creation of Genomics Board

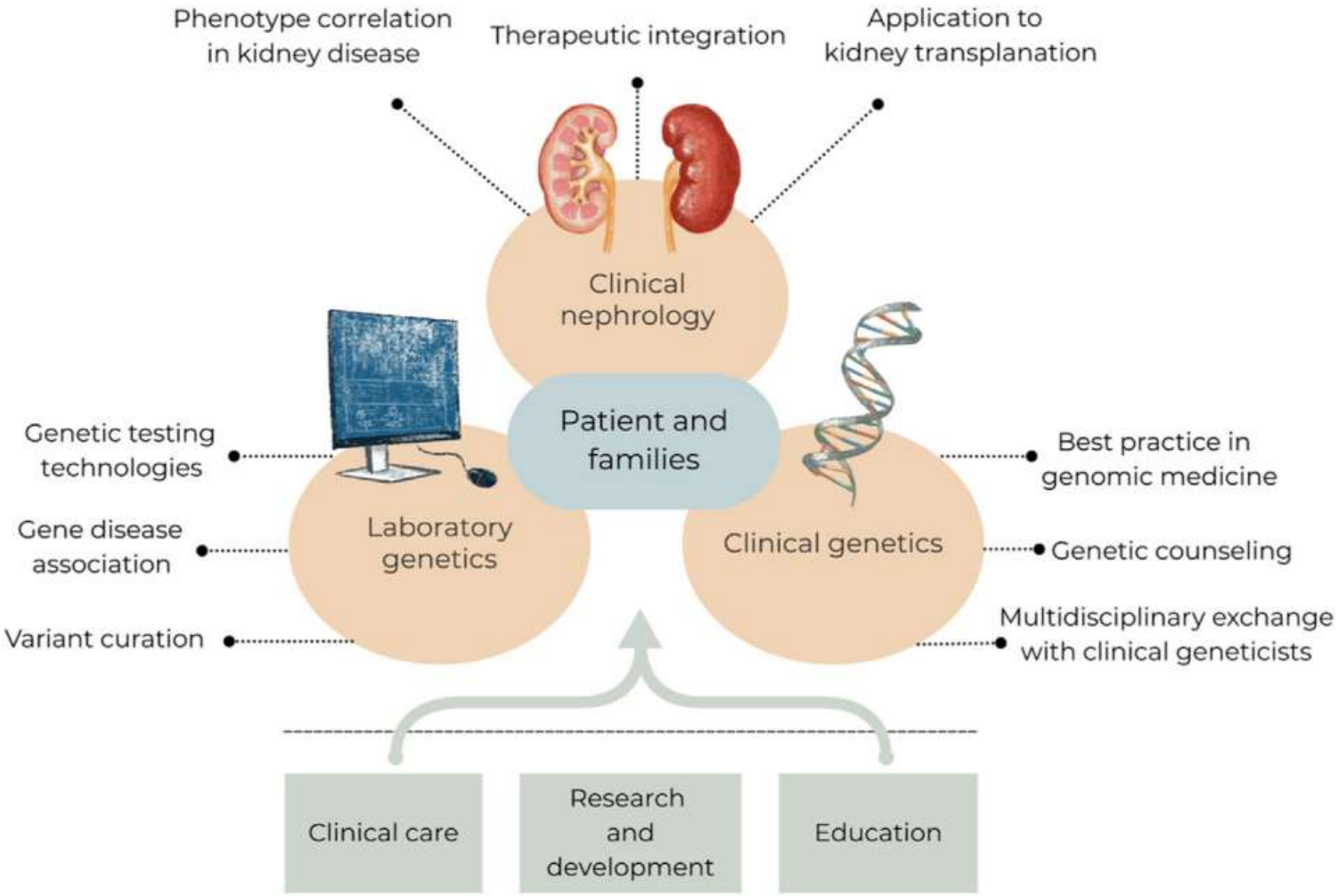
	Constitution of Board	Members	Role
1	**Geneticist/Clinical geneticist**	Dr Preetha /Dr Jainy/ Dr.Anuradha	Interpretation of report; posttest plan/advice
2	**Genomic Analyst**	Dr Ambily / Mr Shivakumar/New appointee	Analysis of genetic data obtained from sequencing
3	**Lab scientist**	Dr Swetha / New appointee	Sequencing based on the test requested and resolving technical queries
4	**Clinical expert**	Dr Anil Vasudevan	Guide and facilitator and provide clinical and bioinformatic inputs
5	**Domain Expert** Neurologist Pediatrician Neuro developmental pediatrician Hematoncologist (Pediatric/Adult) Neonatologist Endocrinologist Cardiologist (Pediatric/Adult)	Faculty deputed by the respective departments	Provide clinical information to help interpret the results

a) Interpretation
b) General advice regarding communication of the report and plan to patients and their families
c) Advice regarding further testing in the index patient & suggested family screening.
d) If a patient needs further clinical evaluation or genetic counselling by the geneticist, clinician can refer the patient to genetics OPD.

Challenges – “Genetic literacy among clinicians”

- **Breadth of knowledge and skill sets in clinical genomics is vast**
- **Kidney medicine brings its own complex layers**
- **Physician knowledge gaps surrounding genetics *[“Genetic literacy”]***
- **Lack of curriculum/specialized training oppurtunities**

Genetic Nephrology: An Arising Subspecialty in Kidney Medicine



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Summary

Enhanced Diagnosis

Genomic testing improves accuracy in diagnosing kidney diseases for better patient care.

Individualize management

Genomic insights enable tailored therapies specific to individual kidney disease profiles.

Innovative Therapeutic Advances

Ongoing genomic research is paving the way for novel kidney disease treatments.


THANK YOU