UMC Utrecht

Genetische aspecten en mictieproblematiek, wat weten we nu echt?

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UMC Utrecht Expert Centre Hereditary and
Congenital Nephrologic and Urologic Disorders

Urotherapie FIGI 20240311

UMC Utrecht NIERSTICHTING Leven gaat voor.

European Reference Network | ERN eUROGEN Rare Urogenital Diseases & Complex Conditions

European Reference Network for rare or low prevalence complex diseases — Network Kidney Diseases (ERKNet) — Member University Medical Center Utrecht — The Netherlands

1

Disclosure belangen spreker

(potentiële) belangenverstrengeling	Geen / Zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
• Sponsoring of onderzoeksgeld	•
• Honorarium of andere (financiële) vergoeding	•
• Aandeelhouder	•
• Andere relatie, namelijk …	•

2

Wie ben ik

- Klinisch geneticus
- associate professor translationele nefrogenetica

3

Belangrijkste take home: overleg!

- Overleg

4

Context

- UMCU Genetics:
  - 29 clinical geneticists
  - 15 laboratory specialists genetics
  - 250 employees
- Netherlands
  - Population of 17,5 million
  - 8 academic hospitals, w. genetics departments
- Clinical Geneticist
  - 4 yr specialty training
  - Patients: preconceptional-prenatal-0-100 yrs

5

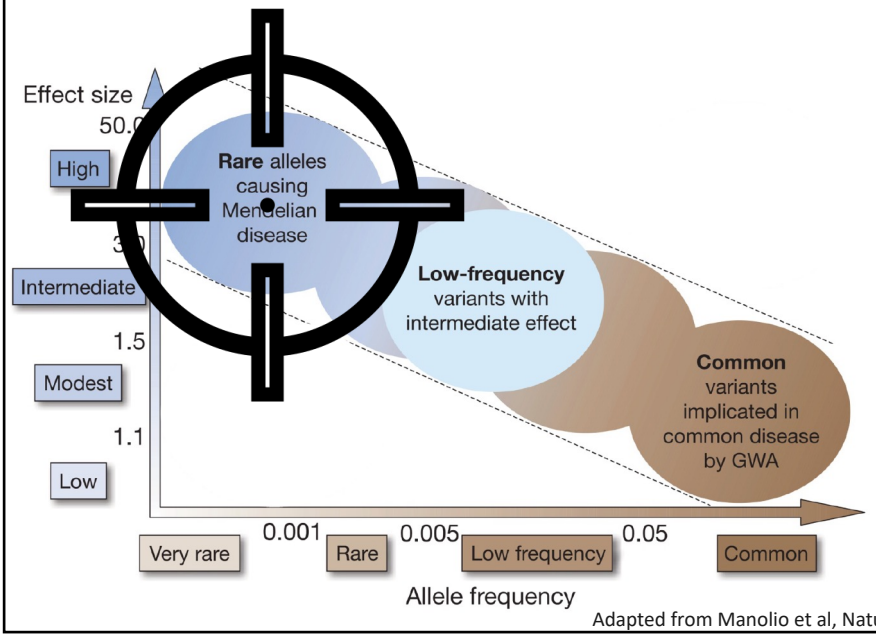
Context genetic care

- Reimbursed from mandatory health insurance:
  - Genetic counseling
  - Genetic testing
- Types of test available (from academic lab):
  - Genepanels (from WES)
  - (trio) WES
  - SNP array
  - Mitochondrial DNA
  - Etc etc
- Who can request
  - organspecialists with enough experience:
    - Single genes / Genepanels in symptomatic patients
  - Clinical geneticists:
    - Presymptomatic patients / broad testing/ complex cases/families / and of course symptomatic

Maaike Wijnands
Studio Oehoe

6

"Hospital genetics": monogenic disorders



Adapted from Manolio et al, Nature 2009

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Received: 11 January 2023 | Revised: 15 March 2023 | Accepted: 18 March 2023
DOI: 10.1111/cge.14331

REVIEW

CLINICAL GENETICS WILEY

The genetics of incontinence: A scoping review

Anders Breinbjerg[1,2] | Cecilie Siggaard Jørgensen[1,2] | Britt Borg[1,2,3] | Søren Rittig[1,2] | Konstantinos Kamperis[1,2] | Jane Hvarregaard Christensen[4,5]

8

how

what

Een gen

'exoom': alle ~20.000 genen

6.000 bekende v. 14.000
onbekende rol
1-2% of the genome

Genpanels

9

Veelvoorkomende spraakverwarring

- Het is niet erfelijk, want ik ben de enige in de familie
- Erfelijk: oorzaak in DNA

10

Belangrijk om te weten over genetisch testen en nefro/uro genetica

- Genetici zijn heel goed in “niet prikken”
  - De verwijsindicatie herkennen is veel belangrijker dan de patient/ouders alles proberen uit te leggen
- (ook grote) genetische tests kunnen als het moet snel gedaan worden (<2 weken)
  - Ook/juist prenataal
- Lang niet alle erfelijke aandoeningen hebben >1 aangedane persoon in de familie
- Expertise centra met (online en multicenter) MDOs
- Een aangeboren afwijking bij een eerder kind is een GUO indicatie in een volgende zwangerschap

- DNA opslaan is makkelijk en makkelijk uit te leggen, zonder consent doen/mogen we er niets mee.

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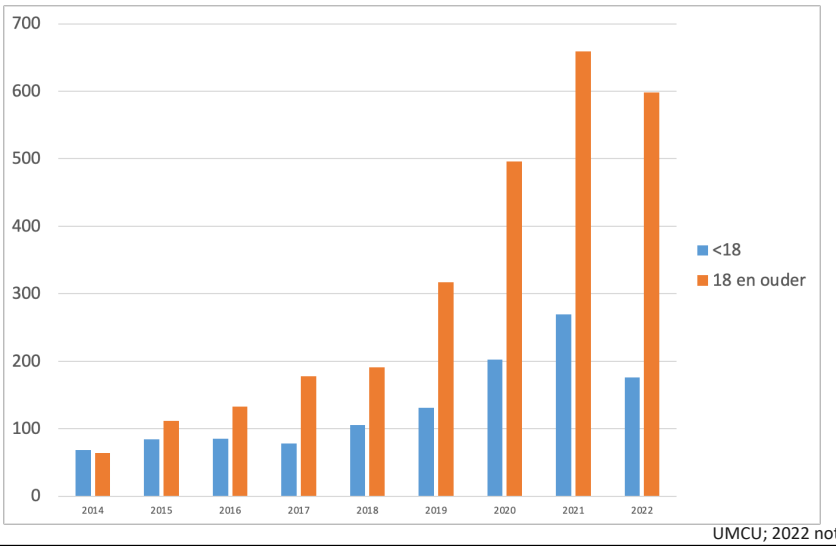
Nephrogenetics genepanels: booming



UMCU; 2022 not complete

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Single-gene kidney disorders:
potential clinical presentations

1. Proteinuria (fault in glomerular structure) ← hematurie
2. Loss of electrolytes, sugar, amino acids (tubular defects)
3. Blobs on ultrasound (cysts & tumours) ←
4. Seen on an X-ray (calculi and nephrocalcinosis) ← Medullaire spons
5. Unusual anatomy (congenital – CAKUT kids) ←
6. Onbegrepen nierziekte/nierfalen

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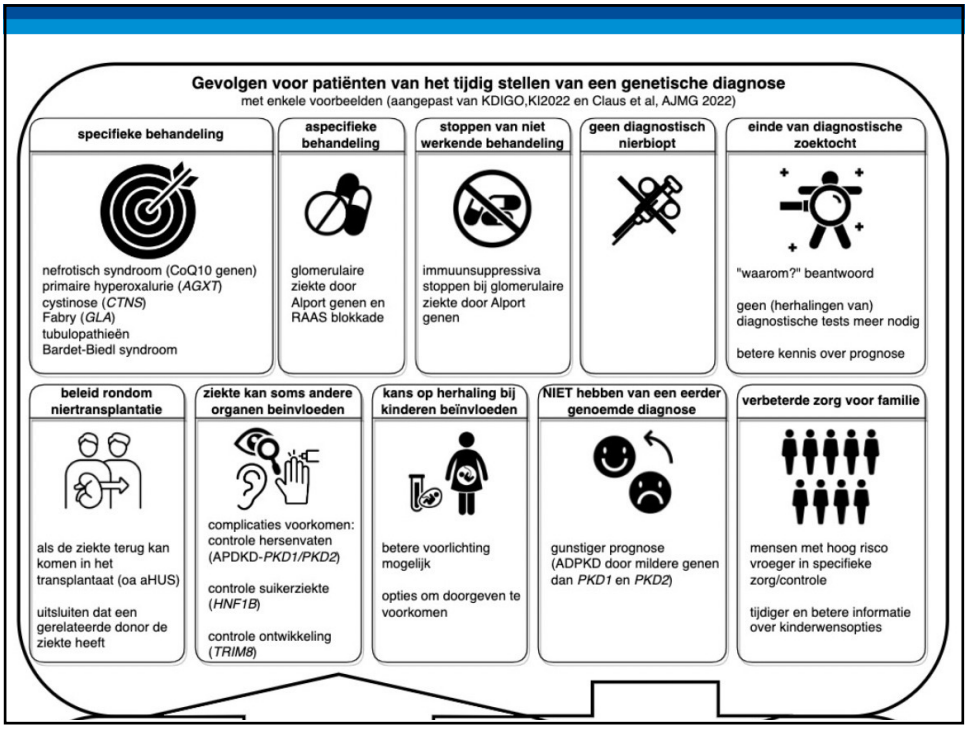

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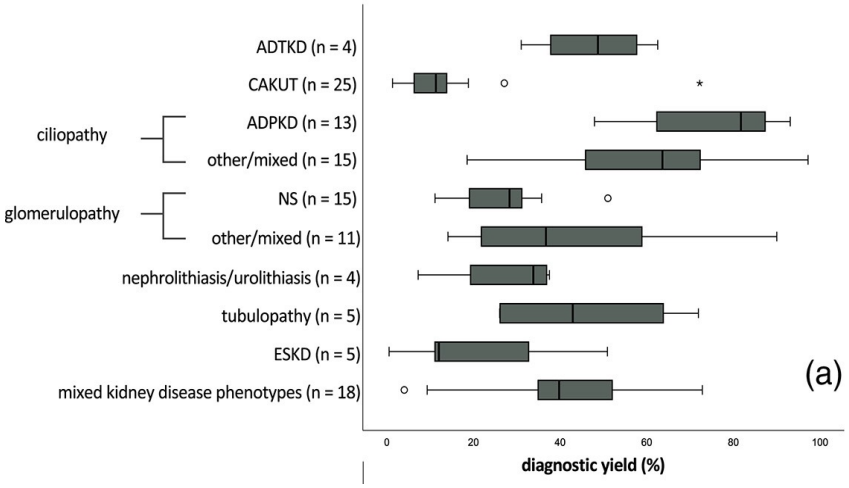
diagnostic yield differs per phenotype group: ranges



- What is optimal yield?

Claus et al AJMG 2022

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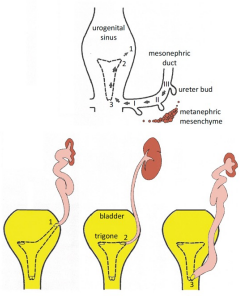
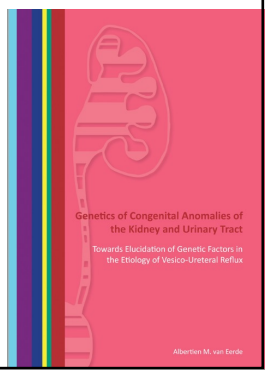
Lagere urinewegen

- CAKUT 'congenital anomalies of the kidney and urinary tract'
  - brede (incl PUV, UPJO, MCDK, etc)
  - vs smalle definitie (gerelateerd aan embryonale ureter budding)
    - VUR
    - renale adysplasie
    - Dubbelsysteem
- LUTO wordt daar soms wel soms niet bij gezet.
- meer functioneel / aansturing/ stevigheid dysfunctional voiding

  verschillende vormen incontinentie





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Een voorbeeld

GENITOURINARY
External Genitalia (Male)
- Cryptorchidism
Kidneys
- Hydronephrosis
Ureters
- Hydroureter
- Urethral valves
- Urethral obstruction
Bladder
- Enuresis
- Urinary tract infection
- Mild neuropathic bladder

- Urofaciaal syndroom (Ochoa syndroom)
- Mutaties in genen die de innervatie (van de blaas) beinvloeden

Oa Daly et al AJHG 2010

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DD

Differential diagnoses, all of which lack the facial features of UFS
Hinman–Allen syndrome, or non-neurogenic neurogenic bladder (identical urinary tract features to UFS)
Primary vesicoureteric reflux accompanied by severe bladder dysfunction
Posterior urethral valves or urethral atresia (anatomical lesions obstructing the urethral lumen are present)
Prune belly, or Eagle–Barrett, syndrome (probably not a single disease [3]); wrinkled skin over distended abdomen; absent or thin anterior abdominal muscles; persistent megabladder postnatally (sometimes with hypocontractile detrusor and undescended testicles)
Megacystis–microcolon–intestinal hypoperistalsis syndrome (wrinkled skin over distended abdomen with microcolon and dilated small intestines)

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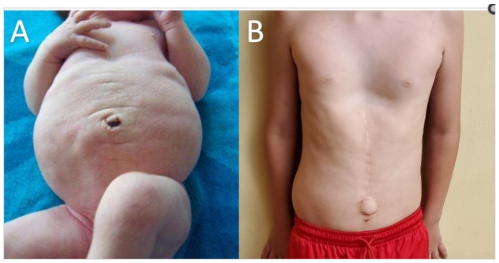
Prune Belly

100100

PRUNE BELLY SYNDROME; PBS



Prune belly syndrome - A. At birth B. At nine years of age (surgical scars noted from a prior abdominoplasty procedure) Contributed by Senthilkumar Sankararaman, MD

INHERITANCE
- Autosomal recessive

HEAD & NECK
Eyes
- Impaired pupillary constriction to light

Mouth
- Dry mouth

ABDOMEN
External Features
- Visible intestinal pattern (so-called 'prune belly', in some patients)
- Thin, lax, protruding abdominal wall (in some patients)

Gastrointestinal
- Constipation

GENITOURINARY
Internal Genitalia (Male)
- Cryptorchidism (in some patients)

Kidneys
- Hydronephrosis

Ureters
- Hydroureter

Bladder
- Distended bladder
- Hyporeflexic bladder
- Areflexic bladder
- Posterior urethral valve

- Mutaties in CHRM3 CHOLINERGIC RECEPTOR, MUSCARINIC, 3

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Megablaas microcolon

MEGACYSTIS-MICROCOLON-INTESTINAL HYPOPERISTALSIS SYNDROME 1; MMIHS1

- MYOSIN LIGHT CHAIN KINASE; MYLK
- Start contractie glad **spierweefsel**

INHERITANCE
- Autosomal recessive

ABDOMEN
Gastrointestinal
- Distal microcolon
- Intestinal malrotation
- Ganglia present in mid-ileum

GENITOURINARY
Kidneys
- Hydronephrosis

Ureters
- Hydroureters

Bladder
- Distended bladder

PRENATAL MANIFESTATIONS
Amniotic Fluid
- Polyhydramnios
- Oligohydramnios
- Anhydramnios

Delivery
- Premature labor

MISCELLANEOUS
- Distended bladder seen on prenatal ultrasound
- Generalized subcutaneous edema on prenatal ultrasound
- Intrauterine or neonatal death

MOLECULAR BASIS
- Caused by mutation in the myosin light chain kinase gene (MYLK, 600922.0003)

20

191800

BLADDER DYSFUNCTION, AUTONOMIC, WITH IMPAIRED PUPILLARY REFLEX AND SECONDARY CAKUT; BAIPRCK

Alternative titles; symbols

URINARY BLADDER, ATONY OF

Phenotype-Gene Relationships

Location	Phenotype	Phenotype MIM number	Inheritance	Phenotype mapping key	Gene/Locus	Gene/Locus MIM number
15q25.1	Bladder dysfunction, autonomic, with impaired pupillary reflex and secondary CAKUT	191800	AR	3	CHRNA3	118503

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Genen database (OMIM) query

- Search ((((((((((hydroureter[Clinical Synopsis]) OR bladder[Clinical Synopsis]) OR urethral valve[Clinical Synopsis]) OR urethral obstruction[Clinical Synopsis]) OR enuresis[Clinical Synopsis]) OR urinary tract infection[Clinical Synopsis]) OR neuropathic bladder[Clinical Synopsis]) OR vesicoureteric reflux[Clinical Synopsis]) OR voiding dysfunction[Clinical Synopsis])) AND "has locus"[Properties]) AND "has symbol"[Properties]) NOT "prefix none"[Properties]

- 183 genen/syndromen
- natuurlijk vaak meer aan de hand

- Oa
  - Bindweefselaandoeningen
    - EDS
  - NB chromosoom afw (oa tris 21)

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Bekende genen voor lagere urinewegen: staan op het CAKUT panel

- Echter als (veel) meer aan de hand, dan vaak keuze voor breder onderzoek

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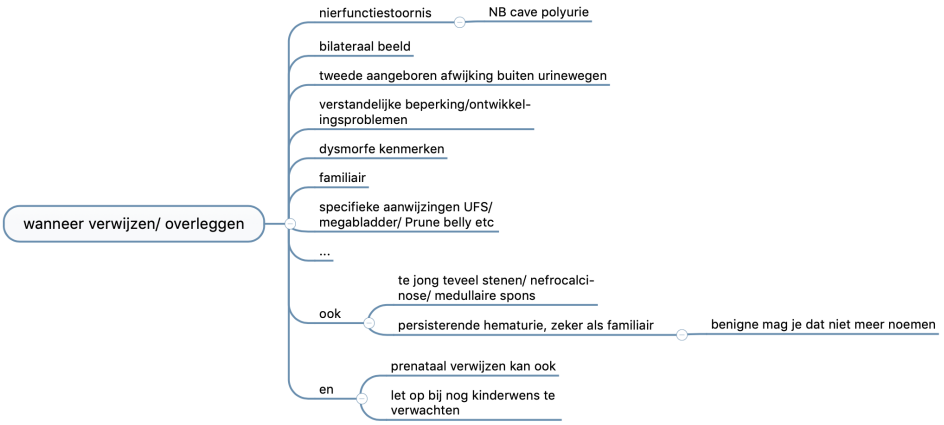
Overleggen/verwijzen (suggesties)

- Let vooral op bij patienten die geen indicatie hebben voor een (kinder) nefroloog
- Overleggen voor minder kan ook



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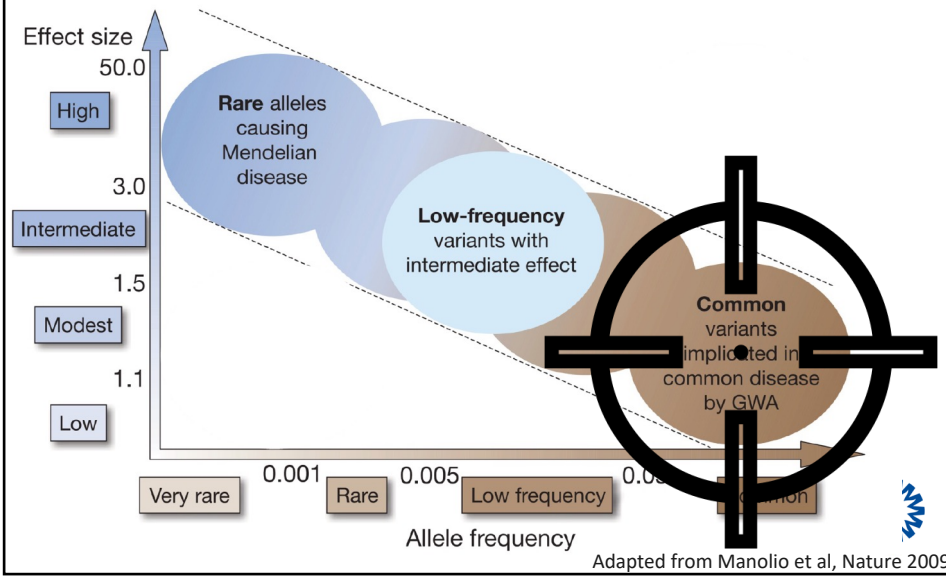
Ook genetica: GWAS



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THE LANCET
Child & Adolescent Health

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ARTICLES | VOLUME 5, ISSUE 3, P201-209, MARCH 2021 | Download Full Issue

Identification of genetic loci associated with nocturnal enuresis: a genome-wide association study

Cecilie S Jørgensen, MD • Henriette T Horsdal, PhD • Veera M Rajagopal, PhD • Jakob Grove, PhD • Thomas D Als, PhD • Konstantinos Kamperis, PhD • et al. Show all authors

Published: January 14, 2021 • DOI: https://doi.org/10.1016/S2352-4642(20)30350-3 • Check for updates

Ook 'gewone' incontinentie is voor een deel erfelijk bepaald, maar waarschijnlijk laag risico factoren

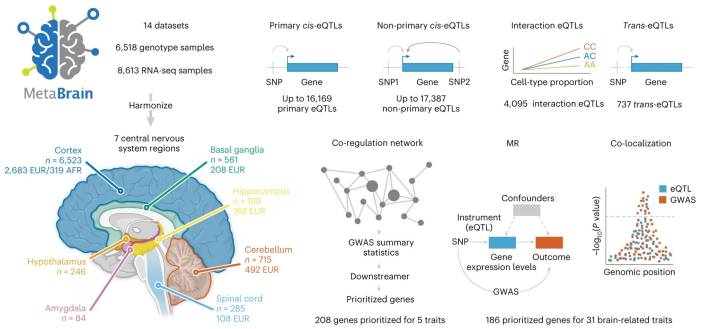
26

Toekomst voor veel voorkomende laag risico factoren

- Meer meer meer (patienten en controles)
- En slimme combinaties met andere datasets

Fig. 1: Overview of the study.

From: Brain expression quantitative trait locus and network analyses reveal downstream effects and putative drivers for brain-related diseases



We downloaded publicly available RNA-seq and genotype data from 14 different datasets consisting of 8,613 RNA-seq measurements from seven main brain regions and 6,518 genotype samples. We created six eQTL meta-analysis datasets and performed *cis*-, *trans*- and interaction-eQTL analyses, built a brain-specific gene co-regulation network and prioritized genes using MR, co-localization and the co-regulation network. Image of sagittal cut of brain created with BioRender.com. This figure summarizes values from Supplementary Tables 1, 3, 8, 12 and 25–30.

De Klein et al, Nature Genetics 2023

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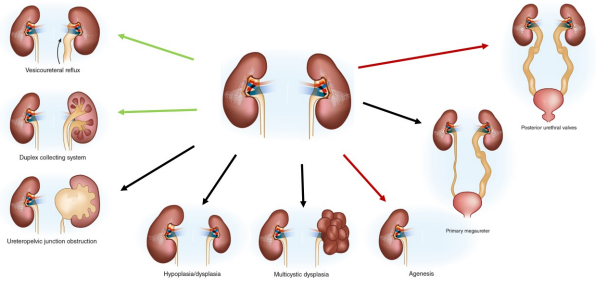
Ons nierstichting consortium

ArtDECO

Aetiology of **r**enal and urinary **t**ract anomalies defines **D**iagnostic **E**fficacy and **C**linical **O**utcome



***CAKUT = Congenital Anomalies of the Kidney and Urinary Tract**

After: Westland et al. *Clin J Am Soc Nephrol* 2020

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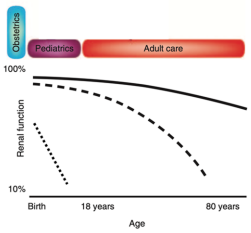
The knowledge gap

CAKUT = ~40% of children with kidney failure

BUT

Kidney survival differs between CAKUT patients



PROBLEM: Clinical decision-making in CAKUT patients is hampered by

1) largely unknown aetiology of disease
2) unpredictable long-term clinical outcome

Weaver et al. *Pediatr Nephrol* 2017
Wühl et al. *Clin J Am Soc Nephrol* 2013
Adapted from: Chevalier. *Kidney Int* 2009

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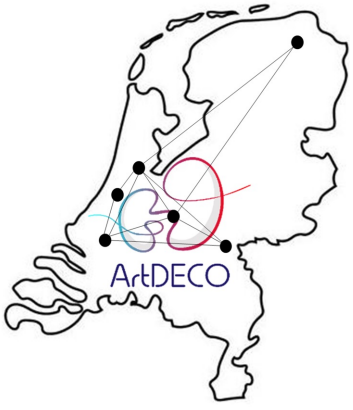
Our Team

+40 supporting scientists!



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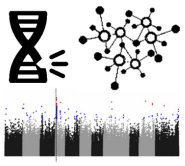
ArtDECO

WP1. Establishment of a nationwide CAKUT data- and biobank

WP2+3. Gene discovery using innovative statistical analyses



WP4. Complex aetiology and gene-environment interactions

WP5. Patient-friendly functional modelling of novel genetic and environmental factors

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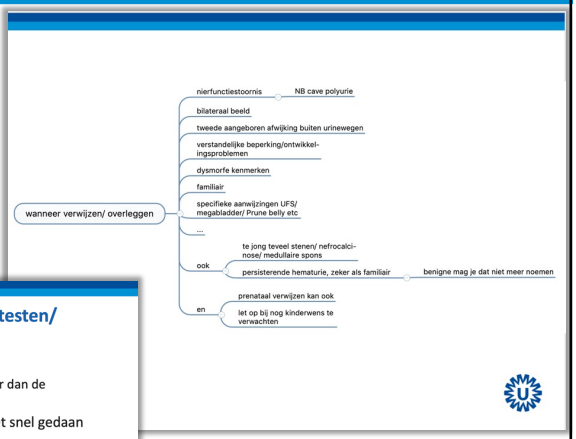
Take home

- bewustzijn
- OVERLEG



Belangrijk om te weten over genetisch testen/ nefro/uro genetica

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- DNA opslaan is makkelijk en makkelijk uit te leggen, zonder consent doen we er niets mee.

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UMCU Expert Centre Hereditary and Congenital Nephrologic and Urologic Disorders

Nephrogenetics Group
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Marijn Stokman
Laura Claus
Margriet Gosselink
Iris Lekkerkerker
Team GeNepher

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Gijs van Haaften
Bert vd Zwaag
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Laetitia de Kort

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Roos Masereeuw

Exp. Nephrology
Gisela Slaats
Carla Pou Casellas

Nierpatiënten Vereniging Nederland
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ERKNet The European Rare Kidney Disease Reference Network

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Transplantlines group

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Roos Marsman (AUMC)
Patrick Rump (UMCG)
Online MD meeting partic.

vaneerde@umcutrecht.nl

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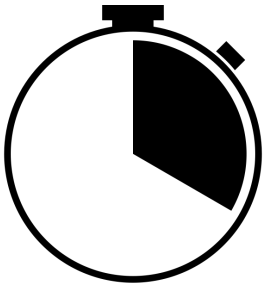
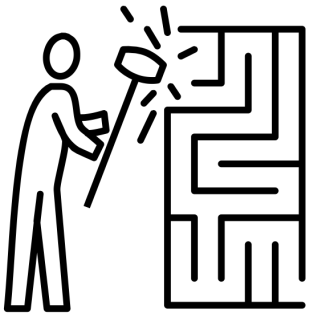
Genetic tests : limited time: calls for (over)simplification





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a gene

all ~20.000 coding genes

6.000 known v. 14.000 unknown role

1-2% of the genome

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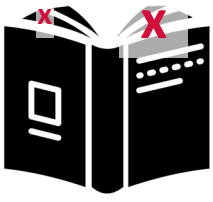
Types of variation

single nucleotide variation

Created by Prithvi from Noun Project

from SNP to pathogenic mutation

copy number



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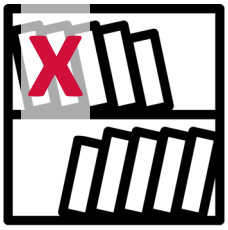

Created by Creative Stall from Noun Project

(repeat expansion, genomic imprinting, chromosomal rearrangement)

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Few types of genetic tests

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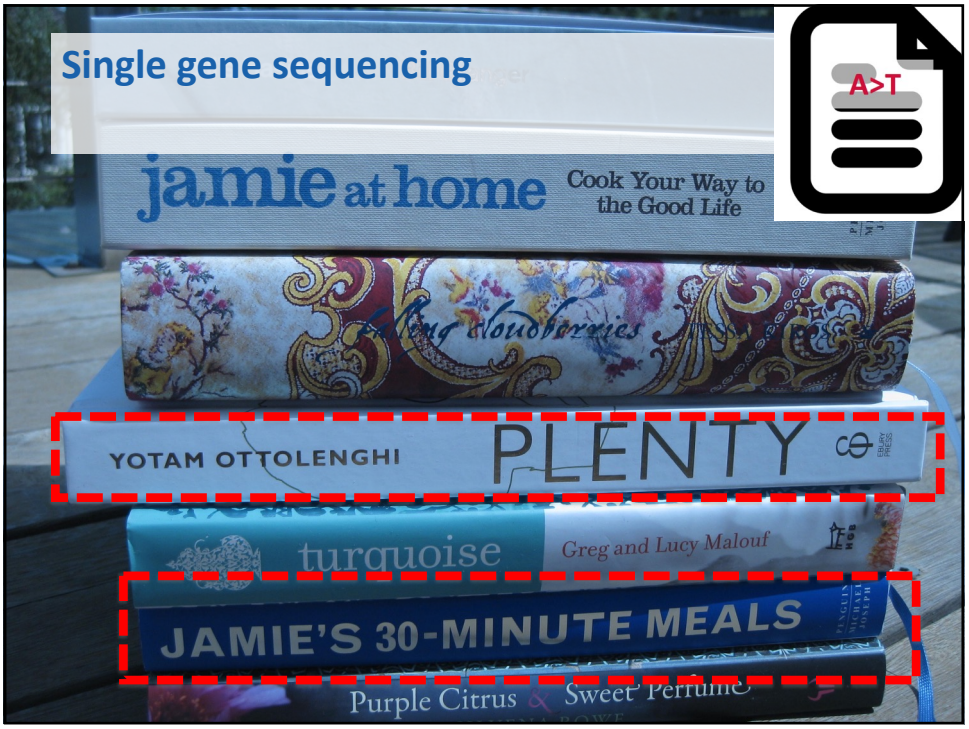
Single gene sequencing



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Next Generation Sequencing (NGS)

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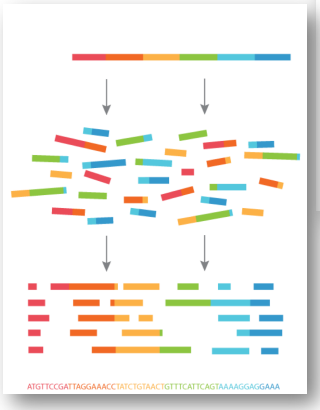
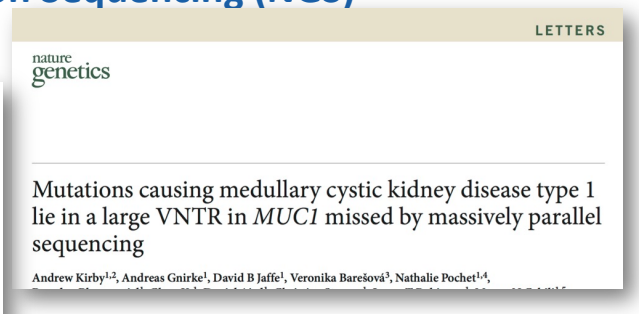
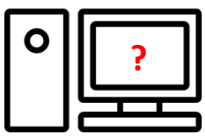
Next Generation Sequencing (NGS)







from: Ibiantech.com

Created by 1211_design
from Noun Project

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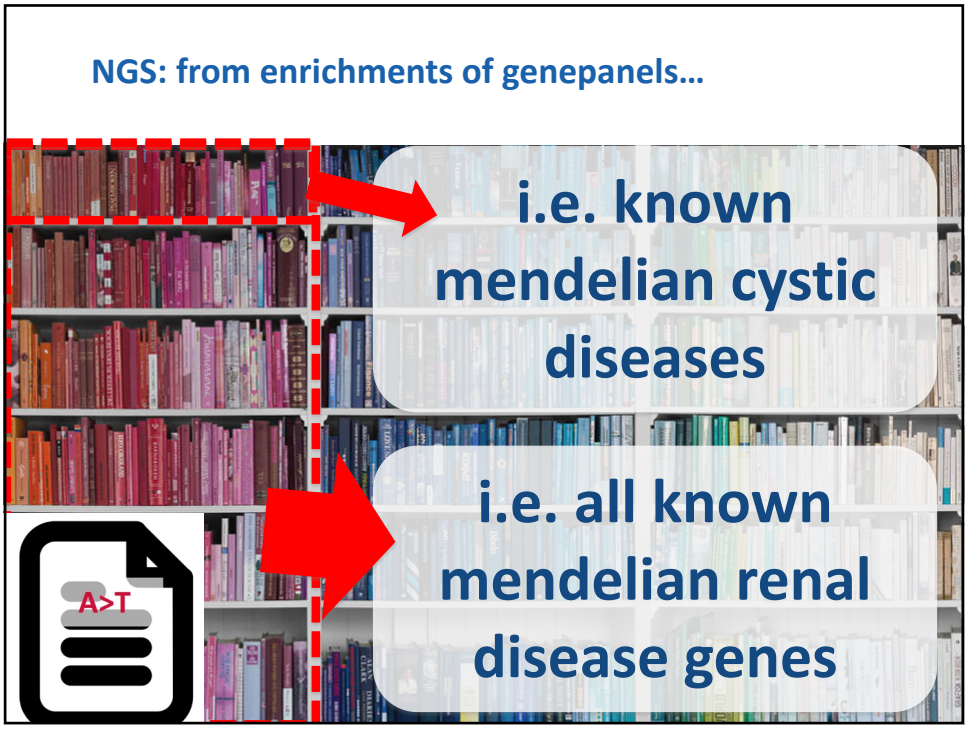
NGS: from enrichments of genepanels…
i.e. known mendelian cystic diseases
i.e. all known mendelian renal disease genes
A>T

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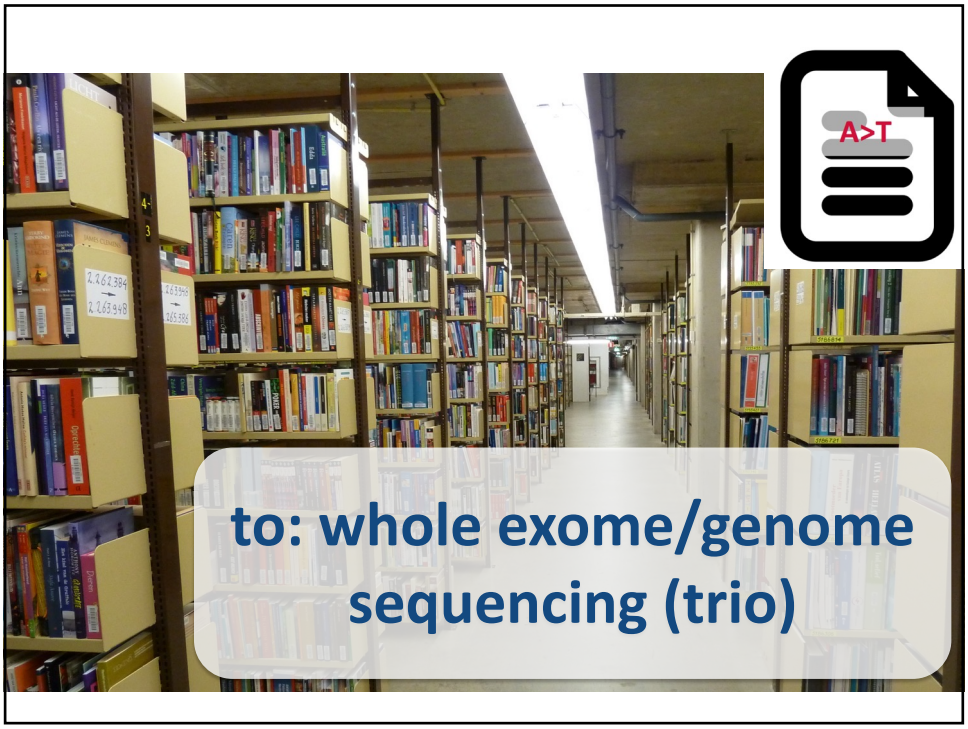
A>T
to: whole exome/genome sequencing (trio)

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A>T
our current practice:
genepanels from WES

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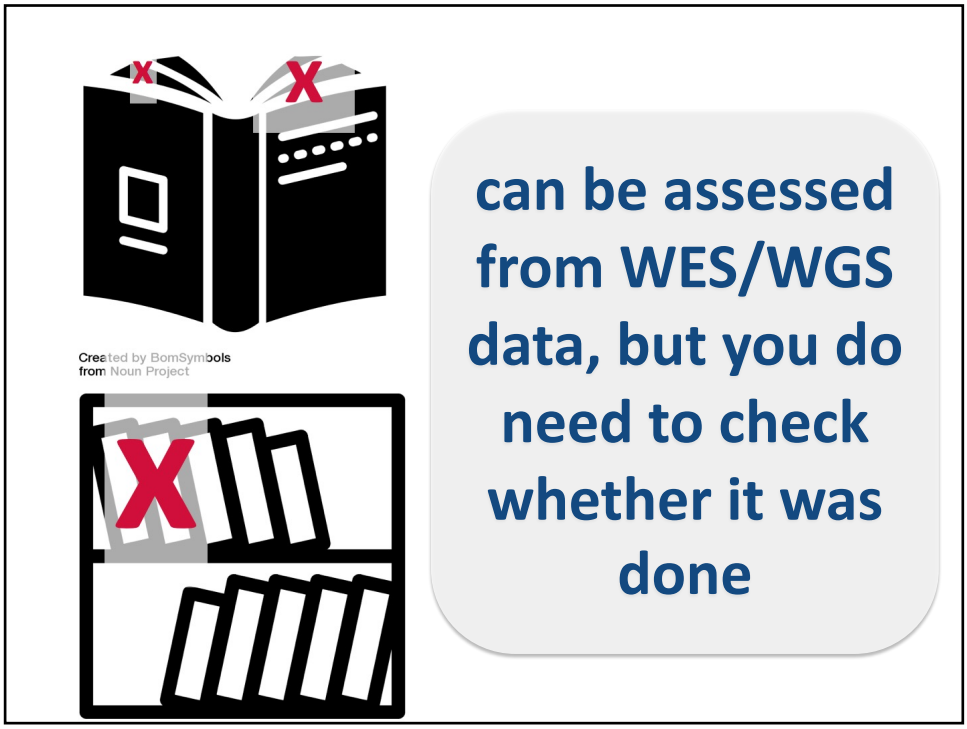
Created by BomSymbols
from Noun Project
can be assessed from WES/WGS data, but you do need to check whether it was done

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