

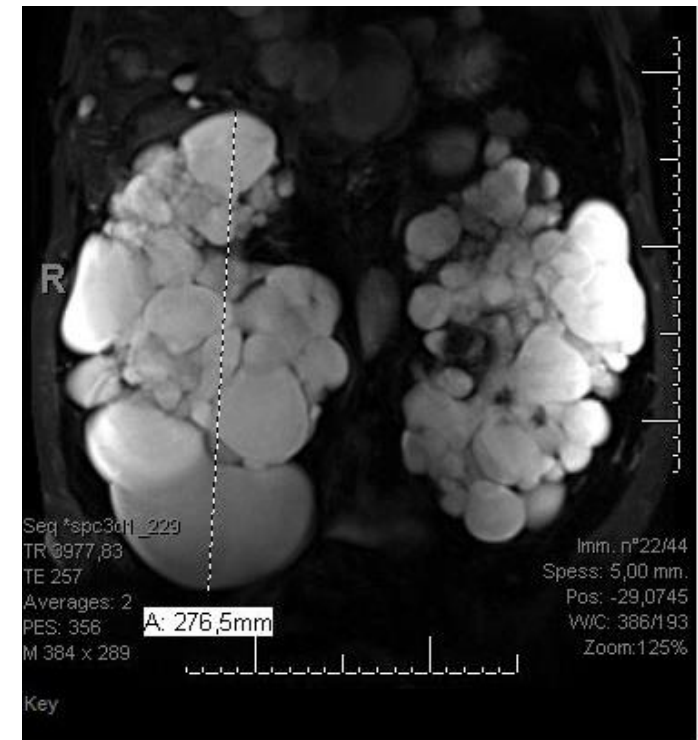
ADPKD:
diagnosi genetica preimpianto (PGT)

Claudia Izzi
medico genetista

U.O Nefrologia e Dialisi e
Dipartimento Ostetrico-Ginecologico
ASST Spedali Civili di Brescia

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

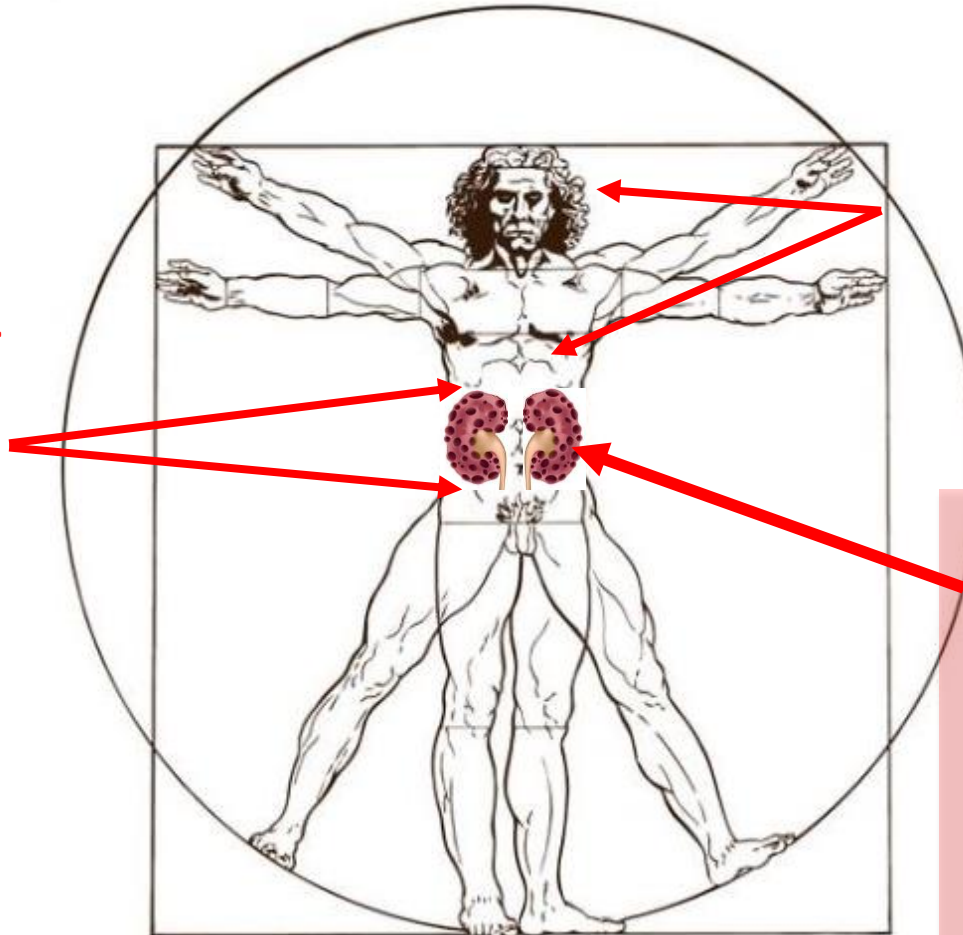
- *Most frequent hereditary late onset kidney disease (12.5 Milion Patients Worldwide)*
- *ADPKD prevalence 1-600/1000*
- *Two Major Genes: PKD1 (85%) PKD2 (15%)*
- *ADPKD1 and ADPKD2 clinical manifestations are indistinguishable*
- *PKD2 is much milder compared to PKD1 with a delayed onset of ESRD of ~20 years²*
- *Characterized by Progressive Enlargement of Kidneys and Renal Failure*
- *Accounts for 5-8% of ESRD worldwide*



AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD): A MULTISYSTEMIC DISORDER

GASTRO- INTESTINAL MANIFESTATIONS

- 1. LIVER CYSTS**
- 2. PANCREATIC CYSTS**
- 3. COLONIC DIVERTICULA**
- 4. HINGUINAL HERNIAS**



CARDIOVASCULAR ABNORMALITIES

- 1. INTRACRANIAL ANEURYSMS**
- 2. CARDIAC VALVE**
- 3. AORTIC ANEURYSMS**
- 4. CORONARY ANEURYSMS**
- 5. LEFT VENTR HYPERTROPHY**

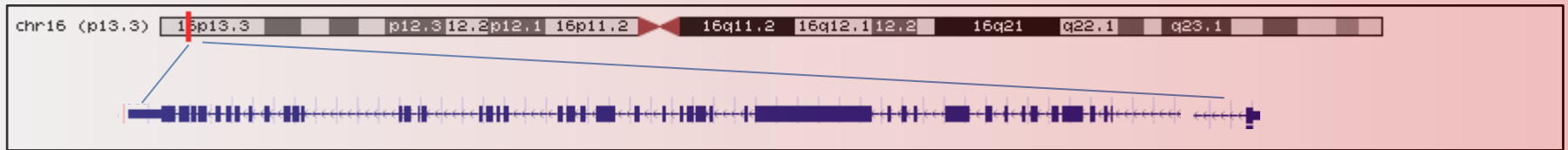
RENAL MANIFESTATIONS

- 1. RENAL CYSTS**
- 2. RENAL PAIN**
- 3. RENAL HEMORRHAGE**
- 4. HYPERTENSION**
- 5. UTI- CYST INFECTION**
- 6. NEPHROLITHIASIS**
- 7. RENAL FAILURE**

ADPKD GENES

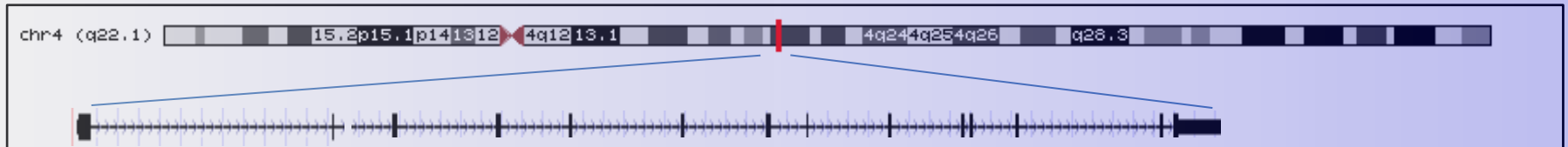
❖ **PKD1 (16p13.3)** ~85% of cases

▪ Encoded protein: **Polycystin 1** (4202 aa)



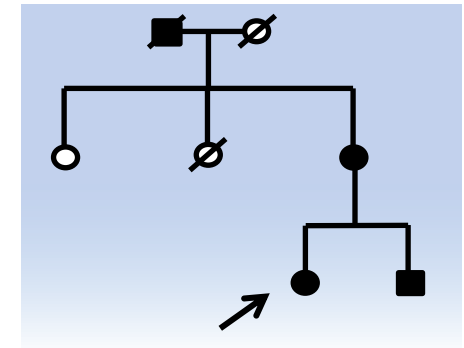
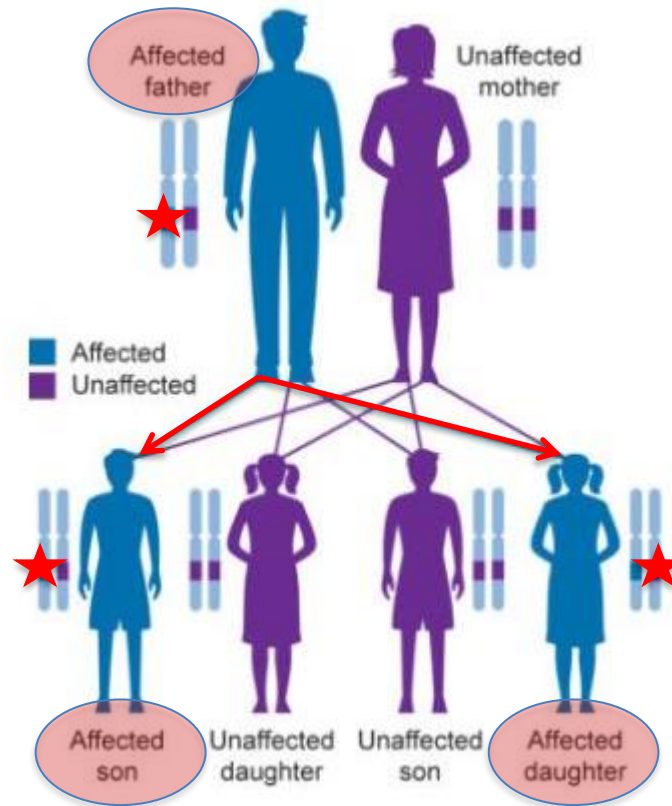
❖ **PKD2 (4q22.1)** ~15% of cases

▪ Encoded protein: **Polycystin 2** (968 aa)



AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

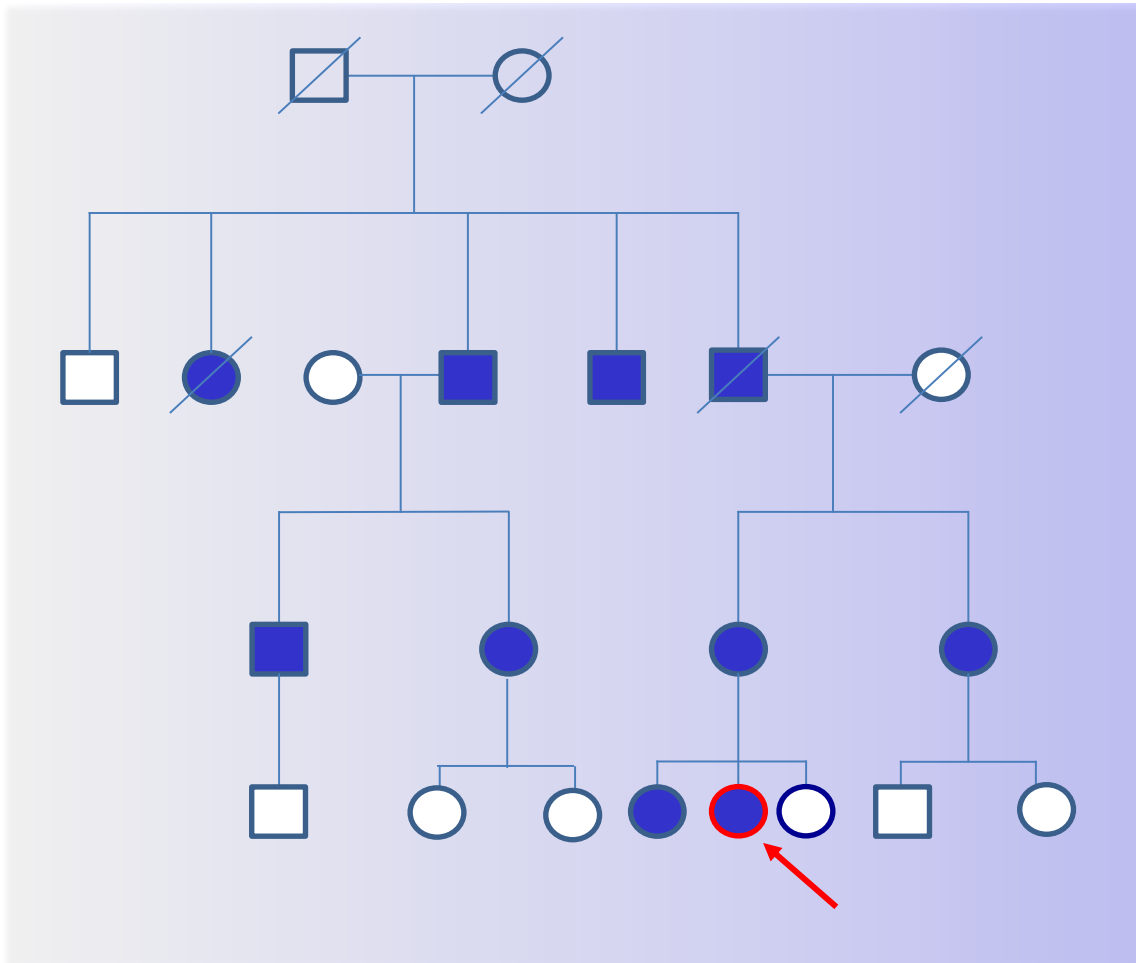
AUTOSOMAL DOMINANT INHERITANCE



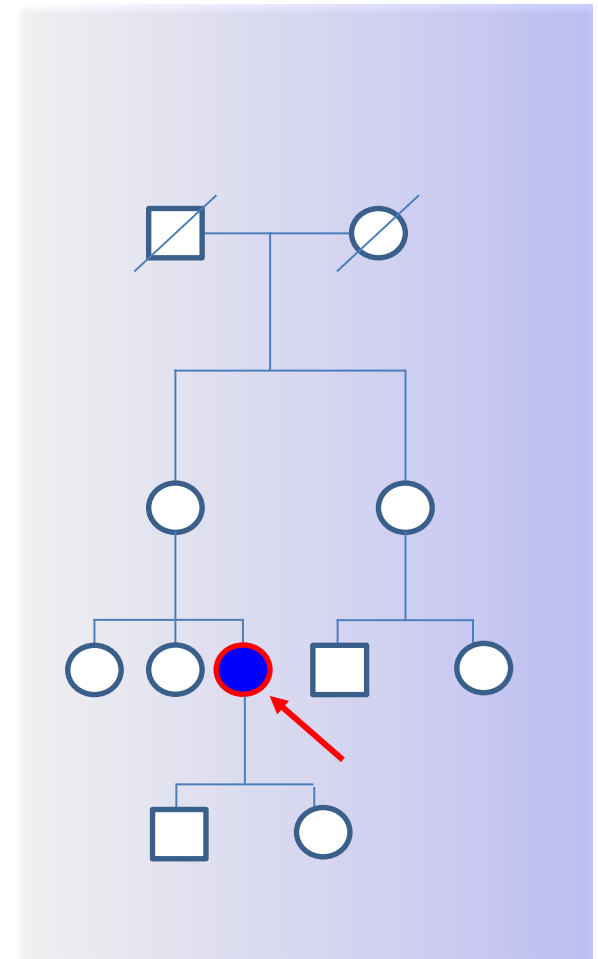
*A person with ADPKD has a **50% CHANCE** of having an affected child with one mutated gene and a 50% of chance of having an unaffected child with two normal genes*

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

FAMILIAL CASES 80-85%



"DE NOVO" 15-20%

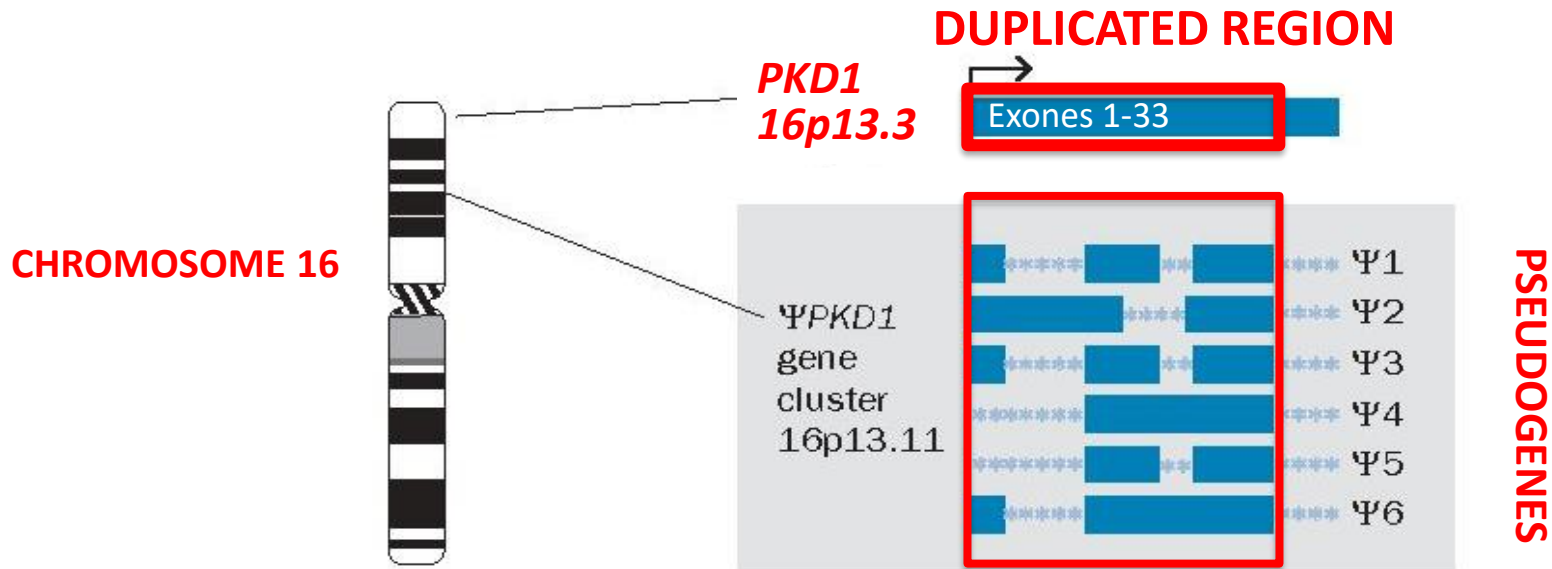
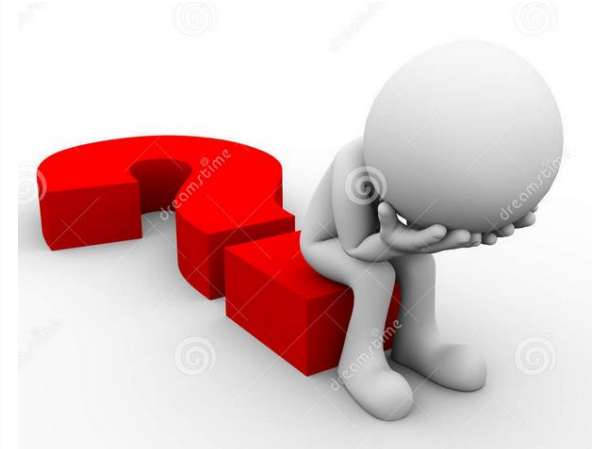


ADPKD GENETIC TEST

- ❖ *Locus Heterogeneity: 2 major genes*
- ❖ *Allelic Heterogeneity: 30% recurrent mutations*
- ❖ *10% of de novo cases*

GENE ANALYSIS

- **PKD2: EASY**
- **PKD1: DIFFICULT!!!**



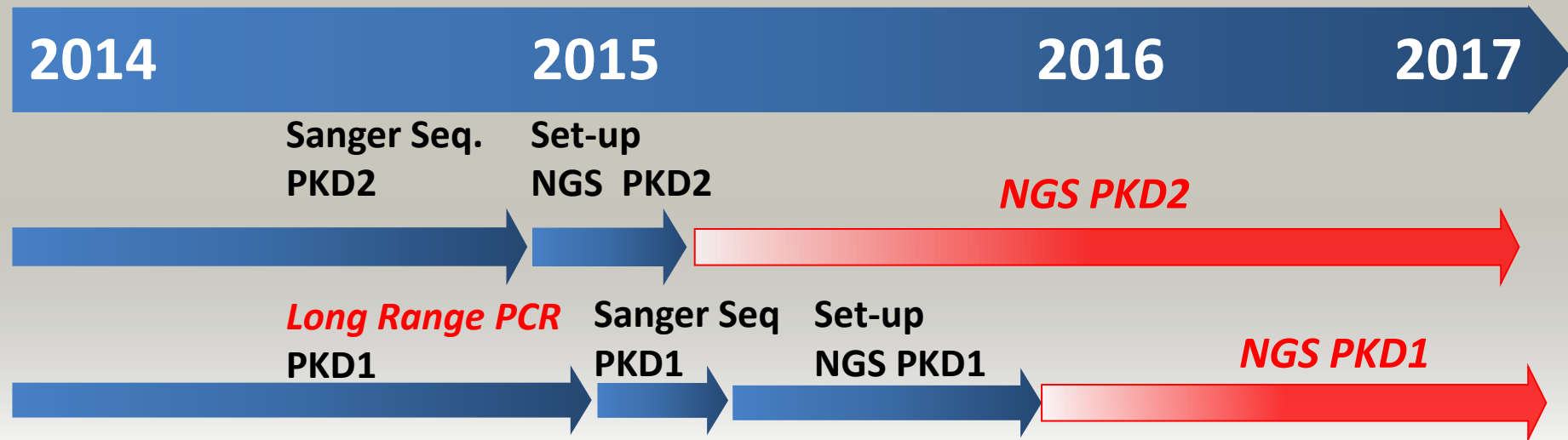
PKD1 and PKD2 GENETIC TEST

Identification of Gene Mutations in Autosomal Dominant Polycystic Kidney Disease through Targeted Resequencing

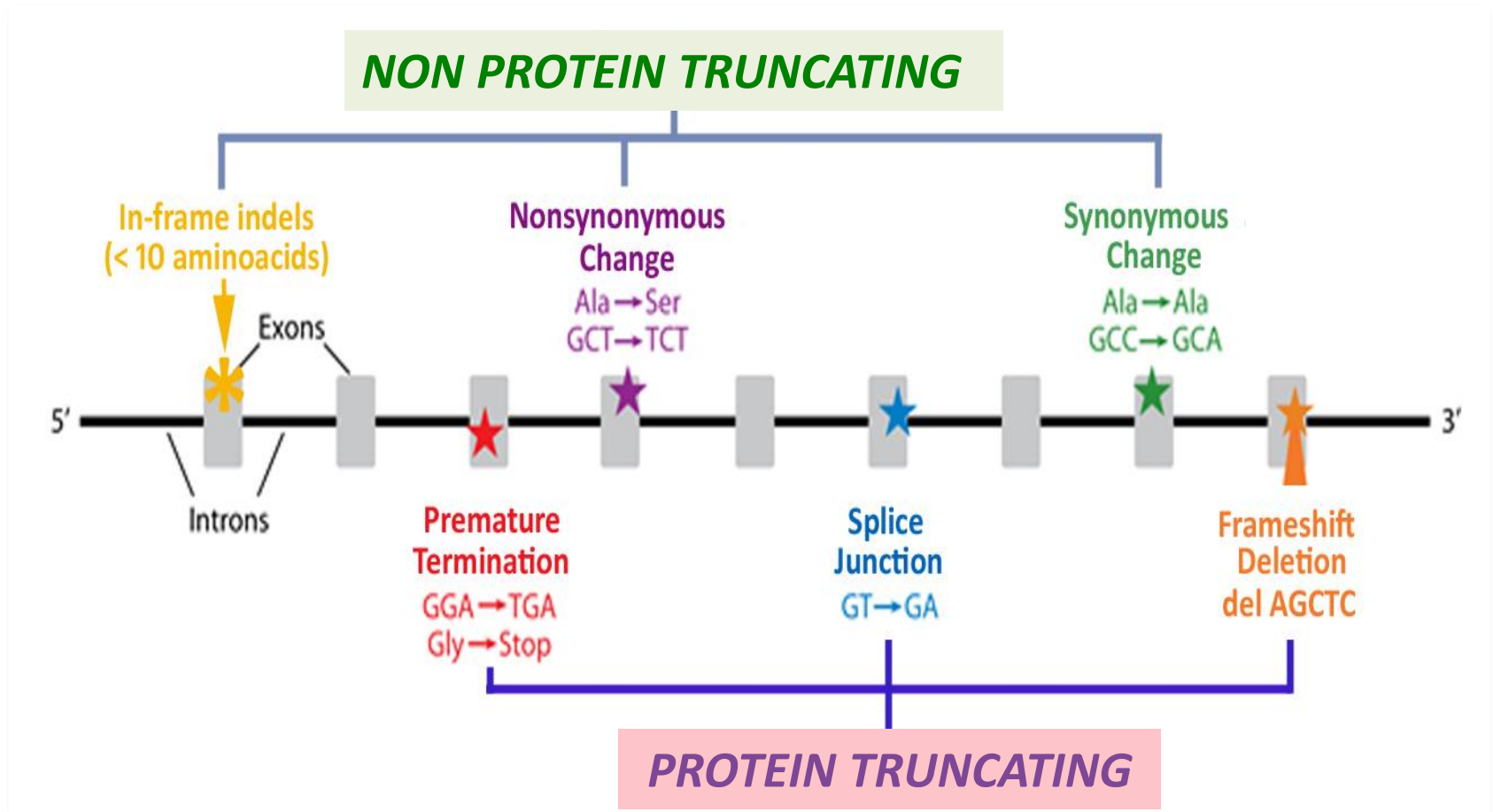
Sandro Rossetti,* Katharina Hopp,[†] Robert A. Sikkink,[‡] Jamie L. Sundsbak,* Yean Kit Lee,[‡] Vickie Kubly,* Bruce W. Eckloff,[‡] Christopher J. Ward,* Christopher G. Winearls,[§] Vicente E. Torres,* and Peter C. Harris*

J Am Soc Nephrol 23: 915–933 **2012** doi: 10.1681/ASN.2011101032

BRESCIA-LAB PKD NGS ANALYSIS SET-UP



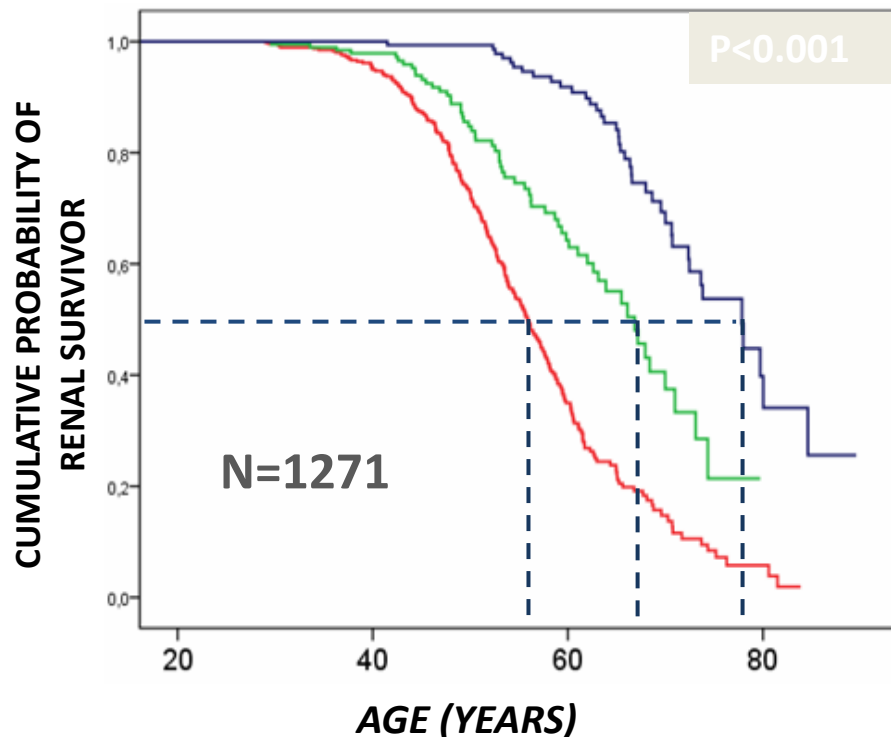
PKD Mutations: effect on Polycystin Function



GENETIC COMPLEXITY IN ADPKD: GENIC AND ALLELIC EFFECT

TYPE OF MUTATION CORRELATES WITH RENAL DISEASE PROGRESSION

GENKYST STUDY-2013



PKD2

PKD2 MUTATION:

MEAN AGE AT ESRD: 77.8 YRS

PKD1

NON TRUNCATING PKD1 MUTATIONS

MEAN AGE AT ESRD: 65.8 YRS

TRUNCATING PKD1 MUTATIONS

MEAN AGE AT ESRD: 55.1 YRS

PKD1/PKD2 variant/mutation patterns

Autosomal Dominant Polycystic Kidney Disease: Mutation Database
<http://pkdb.mayo.edu>



PKD FOUNDATION
Polycystic Kidney Disease

Gene	Mutation	Mutation Type	Clinical Significance	Region	Codon
PKD1: ☒ PKD2: ☐	Germline Only v	All v	Any Pathogenic Mutation v	Exon: ☐ Intron: ☐ 1 v Show All v	 Search

Total Number Of Records Matching Criteria = 1273

1895 = Total Number Of Unique Pedigrees

Unique pedigrees are not recorded for mutations classified as Likely Neutral

PKD1: truncating mutations 75% missense mutations 25%

Gene	Mutation	Mutation Type	Clinical Significance	Region	Codon
PKD1: ☐ PKD2: ☒	Germline Only v	All v	Any Pathogenic Mutation v	Exon: ☐ Intron: ☐ 1 v Show All v	 Search

Total Number Of Records Matching Criteria = 202

438 = Total Number Of Unique Pedigrees

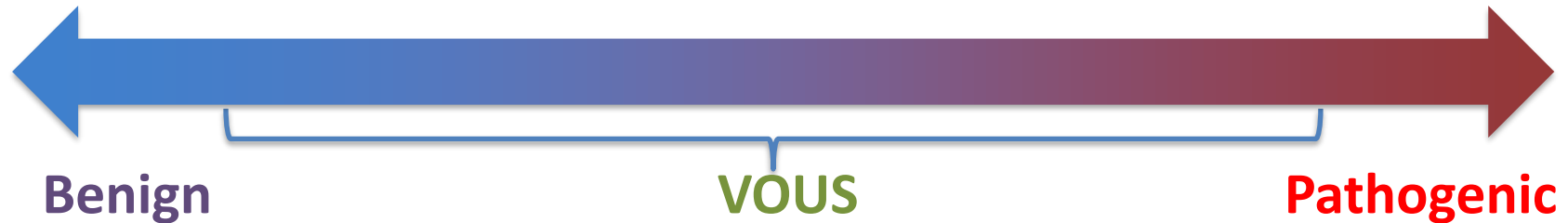
Unique pedigrees are not recorded for mutations classified as Likely Neutral

PKD2: truncating mutations 66% missense mutations 34%

=> Many missense variants are of unknown significance (VUS)

ADPKD NGS RESULTS: INTERPRETAZIONE DELLE VARIANTI

ACMG STANDARDS AND GUIDELINES | Genetics in Medicine



INTERPRETATION OF VARIANTS

Mendelian disease variant terminology

- **Pathogenic**
- **Likely pathogenic** ← (≥90% confidence)
- **Uncertain significance (VUS)**
- **Likely benign**
- **Benign**

Variant not reported in HGMD, locus specific databases, published literature, dbSNP, 1000 Genomes Project, EVS, or ExAC

Variant reported at an **allele frequency insufficient to rule out clinical significance** based on mode of inheritance and severity of disorder

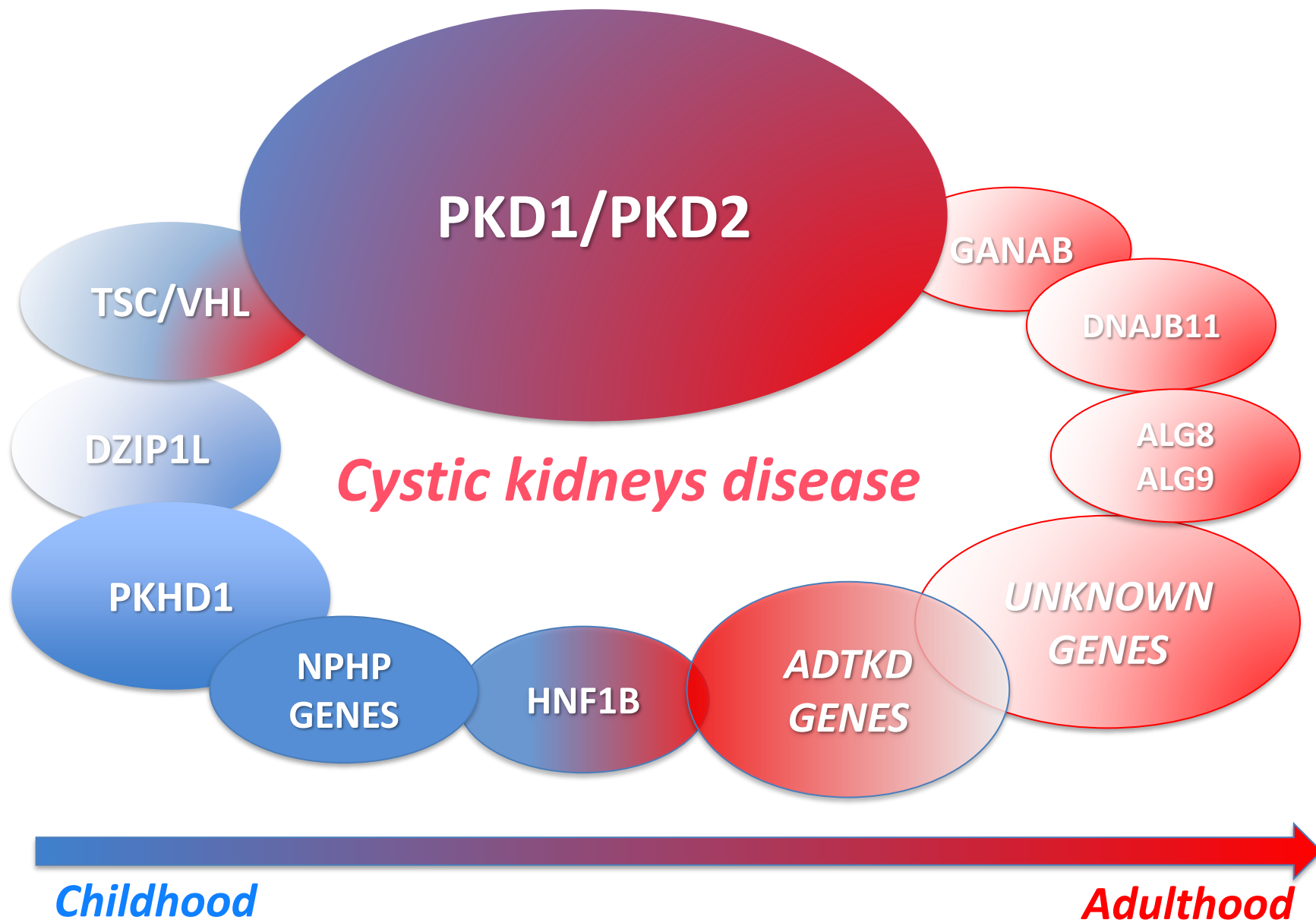
Variant reported in a **single individual** with insufficient segregation or functional data / inadequate clinical information

Evidence from multiple sources is **conflicting** (i.e. evidence for both a pathogenic and benign classification exists)

GENETICALLY UNRESOLVED ADPKD CASES

***6%–11% OF PATIENTS WITH PKD DO NOT HAVE AN IDENTIFIABLE
PKD1 OR PKD2 MUTATION***

- ***missed, fully penetrant mutations*** at the complex, segmentally duplicated *PKD1* locus
- ***mosaicism***
- ***phenocopies*** i.e : autosomal-dominant tubulointerstitial kidney disease (ADTKD)- autosomal dominant polycystic liver disease(ADPLD)
- ***novel PKD genes***



ADPKD:

INDICATION FOR GENETIC TESTING

Table 3. Current and evolving indications for genetic testing in autosomal dominant polycystic kidney disease

Indications for genetic testing in polycystic kidney disease

Scenarios where genetic testing is clinically indicated

- Suspected ADPKD with no apparent family history
- Suspected ADPKD with equivocal kidney imaging findings
- ADPKD exclusion in young (e.g., <25 yr old) at-risk subjects
 - Living related kidney donation evaluation*
 - Obtaining life or disability insurance*

Prenatal and preimplantation genetic diagnosis

Scenarios with evolving indication for genetic testing

- Identifying “high-risk” patients for novel disease modifier therapy or clinical trial
- Delineating the cause of atypical clinical presentation
 - Early and severe disease*
 - Discrepancy between imaging findings and decrease in kidney function*
 - Asymmetric, unilateral, segmental, or lopsided cystic kidneys*
 - Marked intrafamilial disease discordance*
 - Suspected somatic mosaicism*
 - Syndromic forms of polycystic kidney disease*

ADPKD, autosomal dominant polycystic kidney disease. Modified from ref. 49, with permission.

PGT: Preimplantation genetic testing



Diagnosi Genetica Preimpianto - PGT

Raccomandazioni SIGU 2017

per la pratica clinica

GdL SIGU di Citogenetica e Citogenomica

DEFINIZIONE

La diagnosi genetica preimpianto (PGT: Preimplantation Genetic Testing) è un processo che si avvale di tecniche di procreazione medicalmente assistita (PMA) per indagini genetiche su embrioni prima del trasferimento in utero.

PGT: test genetico preimpianto in toto

PGT-M: test genetico preimpianto per malattie monogeniche;

PGT-SR: test genetico preimpianto per anomalie cromosomiche e strutturali

Preimplantation genetic testing in Italy



Diagnosi Genetica Preimpianto - PGT

Raccomandazioni SIGU 2017

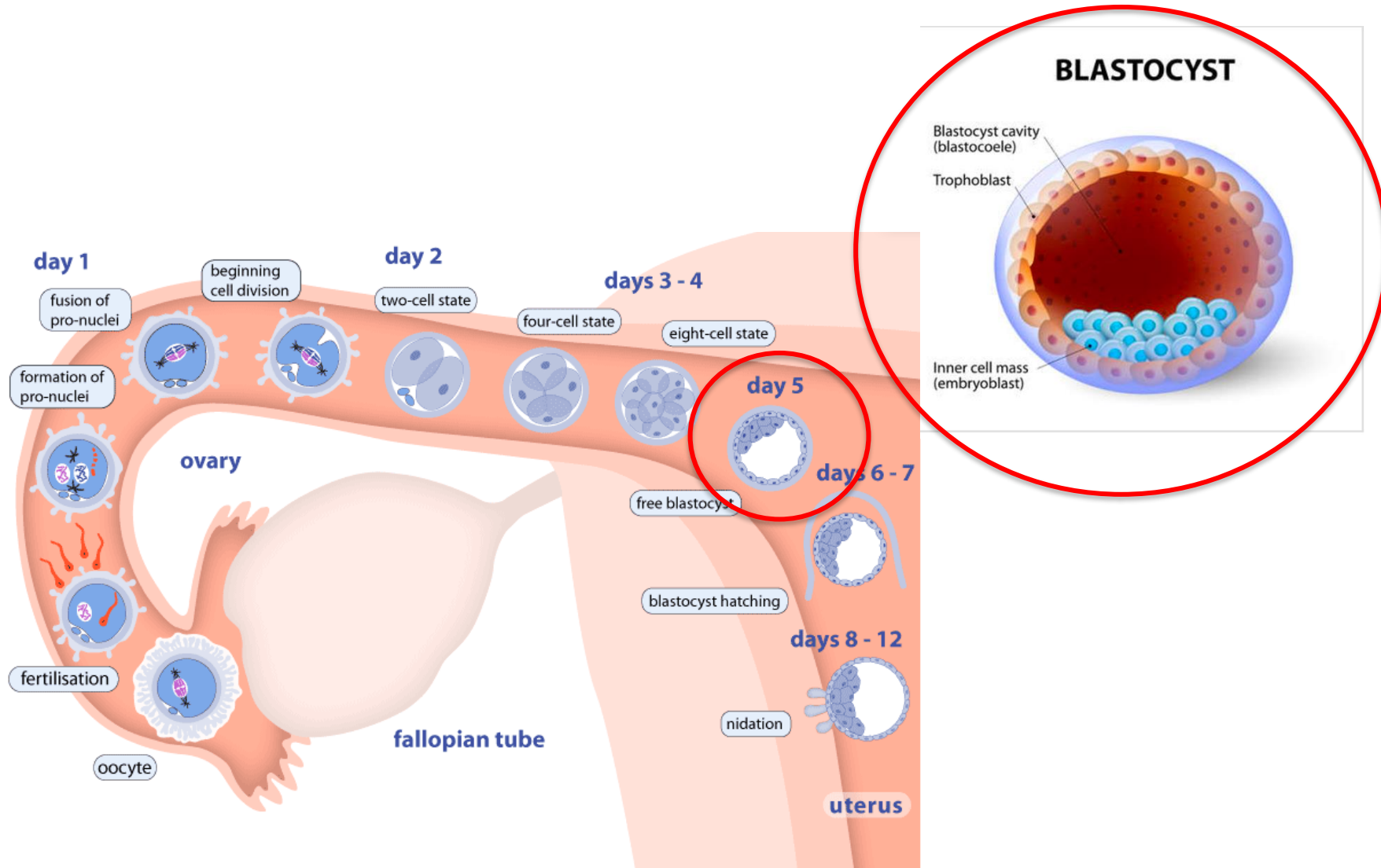
per la pratica clinica

GdL SIGU di Citogenetica e Citogenomica

INDICAZIONI AL PGT-M e PGT-SR

Le indicazioni a PGT-M e PGT-SR sono sovrapponibili a quelle della diagnosi prenatale (DPN) invasiva,
ovvero finalizzate alla diagnosi di una specific grave malattia geneticamente trasmissibile causata da
variazioni del DNA nucleare o mitocondriale, o da una anomalia cromosomica numerica o strutturale. In
dettaglio, la sentenza 229/2015 (riferimento G.U. n. 46 del 18 novembre 2015) ha chiarito che le indicazioni
per il PGT ricalcano quelle della diagnosi prenatale. Pertanto va ribadito come la certificazione sulla
rilevanza della malattia genetica deve essere rilasciata dal Medico del Centro autorizzato (vedi anche
allegato 2 sulla Legittimità giuridica della diagnosi preimpianto).

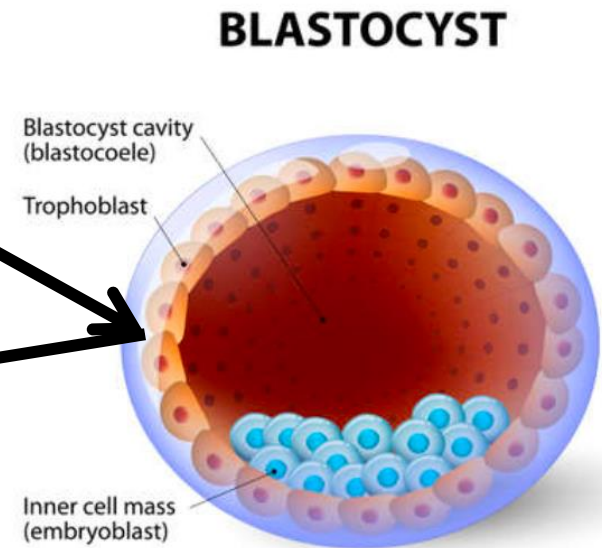
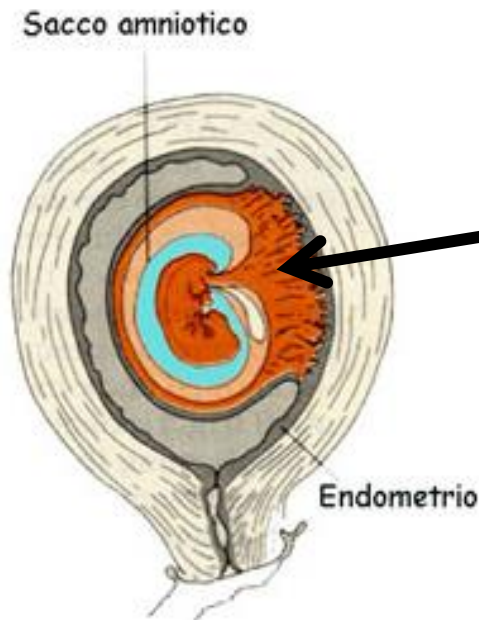
PGT: Preimplantation genetic testing



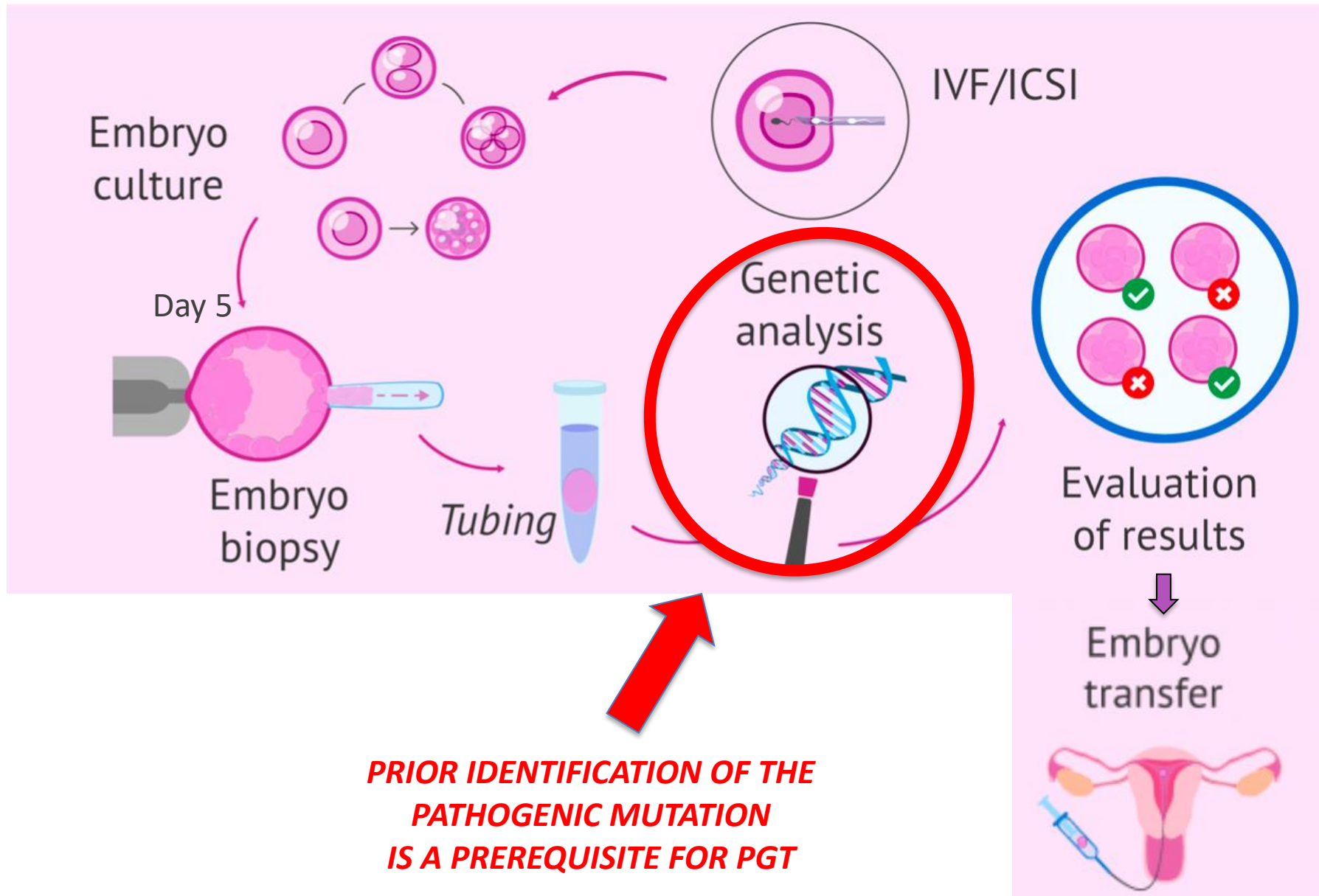
PGT: Preimplantation genetic testing

PGT: only trophoblast analysis

Day 5



PGT: Preimplantation genetic testing



ADPKD-PGT-M first problem

Identifying the disease causing mutation

1. **10%** of patients are GENETICALLY UNRESOLVED
=> *further molecular genetic studies* (Cystic genes panel)
2. **MANY missense** variants are classified as **VUS**

DNA from additional affected family members may be required to determine the pathogenicity of a PKD gene variant

- Family members could be not available
- “de novo” cases

ADPKD-PGT-M second problem

Technical issues for PKD1 gene

The accuracy of PGT is highest when DNA analysis includes both:

1. ***DIRECT MUTATION TESTING***

2. ***HAPLOTYPE RISK ANALYSIS :***

linkage analysis of polymorphic markers closely linked to the PKD1 gene to ensure that there is no allelic drop out.

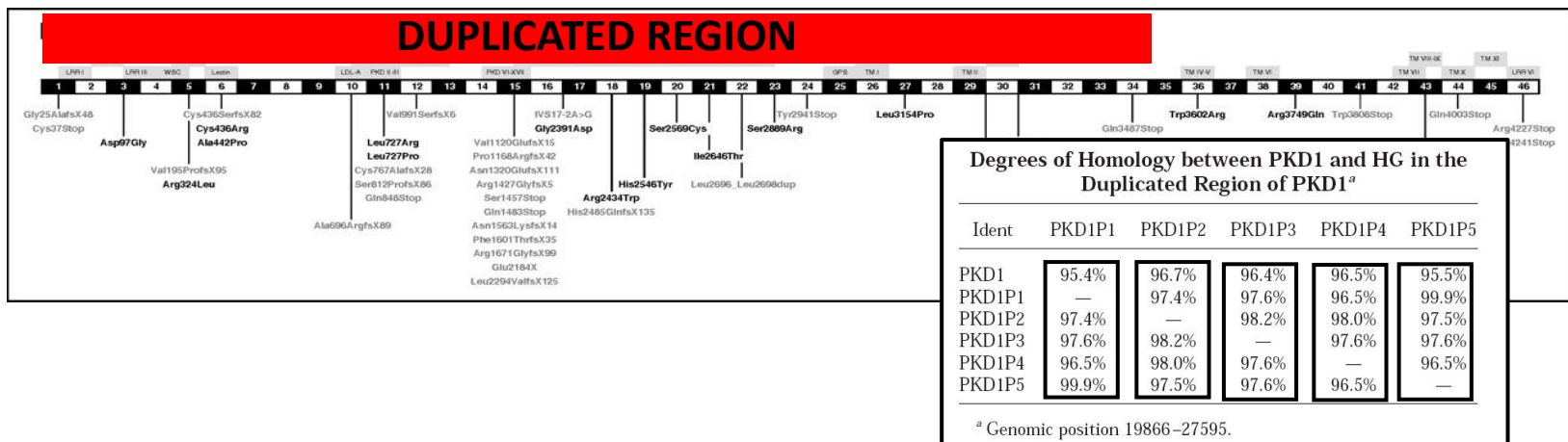
familial ADPKD affected needed for linkage analysis

Technical issues for PKD1 gene

The accuracy of PGT is highest when DNA analysis includes both:

1. DIRECT MUTATION TESTING

NOT POSSIBLE FOR VARIANTS IN THE PKD1 DUPLICATED REGION (EX 1-33)



Most PKD1 variants are located in the first 33 exons

=> Only RISK HAPLOTYPE ANALYSIS

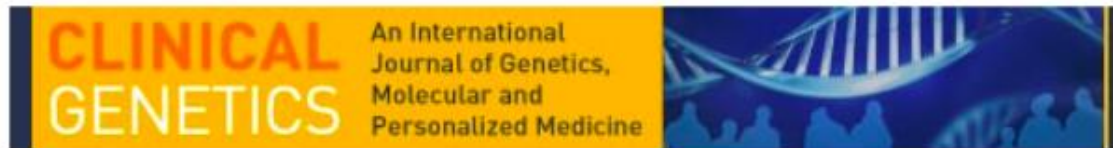
POSSIBLE ONLY IF AFFECTED FAMILY MEMBERS AVAILABLE

ADPKD PGT-M: DE NOVO CASES

IN SPORADIC CASES no familial affected members are available

⇒ RISK HAPLOTYPE ANALYSIS not possible

⇒ *PGT not possible*



ORIGINAL ARTICLE

A novel monogenic preimplantation genetic testing strategy for sporadic polycystic kidney caused by *de novo*PKD1 mutation

Hao Shi, Wenbin Niu, Yidong Liu, Haixia Jin, Wenyan Song, Senlin Shi, Guidong Yao ... [See all authors](#) ✓

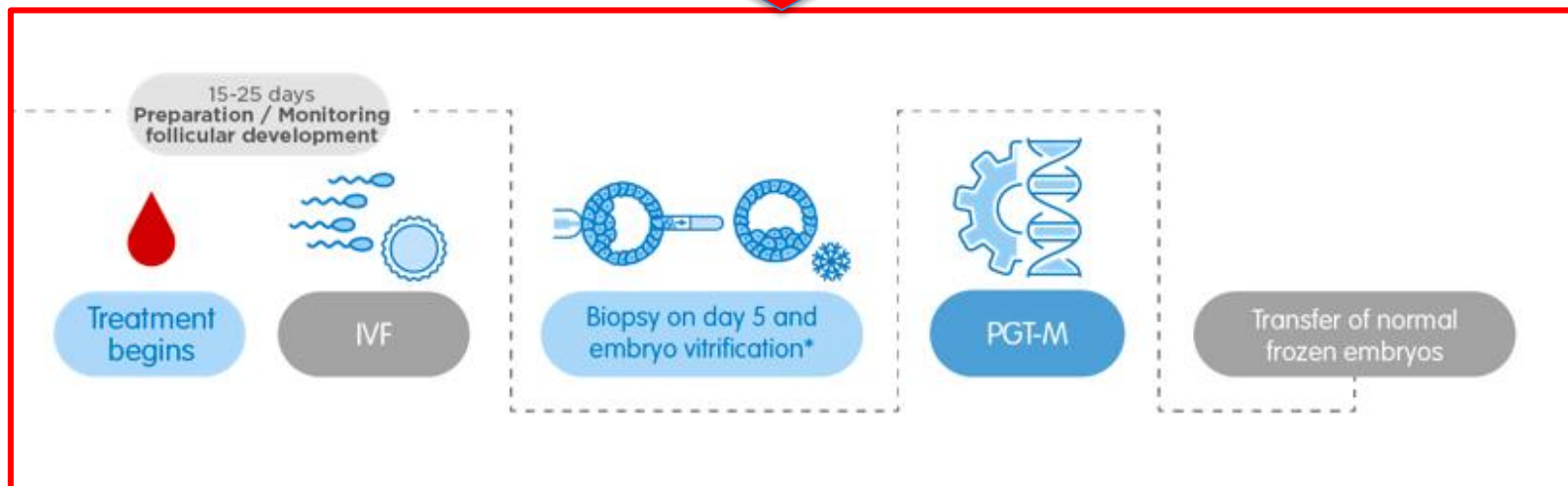
First published: 27 October 2020 | <https://doi.org/10.1111/cge.13871>

Workflow ADPKD PGT-M

1. Nephrogenetic counselling – pre and post genetic test



- 8-12 months**
- SET-UP**
2. PGT-genetic counselling and IVF work-up
 3. Blood or saliva collection of patient and parents for PGD work-up
 4. Identification of informative flanking markers linked with the mutation
 5. Test of the molecular probes and genetic report



ADPKD PGT-M: CLINICAL PROBLEMS

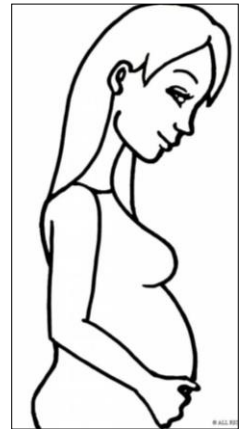
PREGNANCY IN ADPKD WOMEN:

1. Hypertension, reduced renal function and liver cysts:

- risk for ovarian stimulation
- risk related to pregnancy

2. Therapies

- teratogenic drugs



ADPKD AND PGT-M

Case Reports > Fertil Steril. 2004 Oct;82(4):926-9. doi: 10.1016/j.fertnstert.2004.03.041.

Preimplantation genetic diagnosis for polycystic kidney disease

Yury Verlinsky¹, Svetlana Rechitsky, Oleg Verlinsky, Seckin Ozen, Robin Beck, Anver Kuliev

Affiliations — collapse

Affiliation

¹ Reproductive Genetics Institute, Chicago, Illinois 60657, USA.

Preimplantation Genetic Diagnosis Counseling in Autosomal Dominant Polycystic Kidney Disease

Erin L. Murphy, Madeline L. Droher, Miriam S. DiMaio, and Neera K. Dahl

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common hereditary forms of chronic kidney disease. Mutations within *PKD1* or *PKD2* lead to innumerable fluid-filled cysts in the kidneys and in some instances, end-stage renal disease (ESRD). Affected individuals have a 50% chance of passing the mutation to each of their offspring. Assisted reproductive technology using preimplantation genetic diagnosis (PGD) allows these individuals to reduce this risk to 1% to 2%. We assess the disease burden of 8 individuals with ADPKD who have undergone genetic testing in preparation for PGD. Clinical features that predict high risk for progression to ESRD in patients with ADPKD include genotype, early onset of hypertension, a urologic event before age 35 years, and a large height-adjusted total kidney volume. Patients may have a family history of intracranial aneurysms or complications involving hepatic cysts, which may further influence the decision to pursue PGD. We also explore the cost, risks, and benefits of using PGD. All patients with ADPKD of childbearing potential, regardless of risk for progression to ESRD or risk for a significant disease burden, will likely benefit from genetic counseling.

Complete author and article information provided before references.

Am J Kidney Dis. XX(XX): 1-7. Published online Month X, 2018.

doi: [10.1053/j.ajkd.2018.01.048](https://doi.org/10.1053/j.ajkd.2018.01.048)

© 2018 by the National Kidney Foundation, Inc.

8 patients: 5 female; 3 male

- **TYPE OF MUTATIONS**
- **FACTORS AFFECTING PROGRESSION TO ESRD**

ADPKD AND PGT-M

Perspective

Preimplantation Autosomal D

Erin L. Murphy, MD

Autosomal dominant of chronic kidney disease kidneys and in some chance of passing the preimplantation gene assess the disease preparation for PGD ADPKD include genetic large height-adjusted or complications involved also explore the cost potential, regardless benefit from genetic

8 patients

- TYPE
- FACTOR

Table 1. Medical History, Family History, and Genotype of ADPKD Patients Seeking IVF With PGD

Pt	Factors Affecting Progression	Additional History	PKD Mutation*	Risk of Progression to ESRD*
1	• 31 y; F • TKV: 478 mL • htTKV: 304.5 mL/m • HTN • No urologic events	• Innumerable hepatic cysts • Possibly affected maternal grandfather died due to a cerebral hemorrhage at age 48 • Affected mother reached CKD4 in mid-50s	<i>PKD1</i> : c.8978C>T (p.Q2923X) (truncating; not novel)	Genetics score: 3 (high risk); imaging class: 1B (low risk)
2	• 30 y; F • Kidney size on US: 16 cm (R), 17 cm (L) • HTN • No urologic events	• Multiple scattered hepatic cysts • Affected father reached ESRD in mid-40s • Affected paternal aunt died due to a ruptured cerebral aneurysm (late 40s)	<i>PKD1</i> : deletion of exons 27-29 (truncating; novel)	Genetics score: 3 (high risk); imaging class: NA
3	• 39 y; F • TKV: 1,110 mL • htTKV: 730.3 mL/m • HTN • No urologic events	• Innumerable hepatic cysts • Affected father reached ESRD at age 60; received kidney and liver transplant • Affected paternal uncle • Affected brother	<i>PKD1</i> : c.2540C>T (p.Q777X) (truncating; novel)	PROPKD score: 6 (intermediate risk); imaging class: 1C (high risk)
4	• 27 y; F • Kidney size on US: 13.8 cm (R), 14.9 cm (L) • HTN • Persistent flank pain (L)	• No hepatic cysts • Affected mother reached ESRD at age 56	<i>PKD1</i> : c.8537_8532dup11 (p.T2775fs) (frameshift; may be truncating; novel)	PROPKD score: 8 (high risk); imaging class: NA
5	• 32 y; M • Kidney size on US: 11.3 cm (R), 13.2 cm (L) • HTN • No urologic events	• Hepatic cysts • Affected mother has CKD4 (age 59) • Affected maternal grandfather died age 54 • Affected maternal great-grandmother died age 40	<i>PKD1</i> : c.9779G>A (p.G3190R) (likely truncating [near splice site]; novel) <i>PKD1</i> : c.8387C>T (p.S2726S) (silent; likely benign; not novel)	Genetics score: 4 (high risk); imaging class: NA
6	• 32 y; F • Diagnosed at age 6 mo • Imaging NA • HTN • No urologic events	• Affected mother reached ESRD at age 52 • Affected maternal uncle received transplant • Affected maternal grandmother reached ESRD at age 65	<i>PKD1</i> : IVS42-3C>G (likely truncating; novel) <i>PKD1</i> : c.7489T>C (p.S2426S) (silent; likely benign; not novel)	Genetics score: 3 (high risk); imaging class: NA
7	• 37 y; M • TKV: 5,079 mL • htTKV: 2,565.2 mL/m • HTN • No urologic events	• Multiple hepatic cysts • Affected father reached ESRD at age 40; died due to CVA at age 44 • Possibly affected paternal grandfather, died due to CVA, age 45	<i>PKD1</i> : c.7008G>C (p.R2266P) (nontruncating; novel); <i>PKD1</i> : c.355C>G (p.R48R) (silent; likely benign; novel); 18 other <i>PKD1</i> variants and 1 <i>PKD2</i> variant (all likely benign; novel)	PROPKD score: 5 (intermediate risk); imaging class: 1E, (high risk)
8	• 44 y; M • TKV: 3,336 mL • htTKV: 1,774.5 mL/m • HTN • Upper UTI (kidney/ bladder)	• No hepatic cysts • Affected mother	<i>PKD2</i> : deletion of exons 5-15 (truncating; novel)	PROPKD score: 5 (intermediate risk); imaging class: 1D (high risk)

ADPKD PGT: The Netherlands experience

Clinical overview of preimplantation genetic testing for monogenic kidney diseases



Retrospective study



National preimplantation genetic testing expert center



Jan 1995 to June 2019



Couples counseled on preimplantation genetic testing for monogenic kidney disease

n = 98 couples

Most frequent indications for referral are for adult-onset diseases



38% ADPKD



26% Alport Syndrome



9% ARP

Number of referrals steadily increasing since 2009



53% of couples

Opted for preimplantation genetic testing

Of whom 65% experienced at least one live birth



38% of couples

Declined preimplantation genetic testing, for various personal and technical reasons



Conclusions Counselling on preimplantation genetic testing for kidney patients is essential to allow patients to make their own choice. If couples proceed with preimplantation genetic testing outcomes are generally favorable.

Rozemarijn Snoek, Marijn F. Stokman, Klaske D. Lichtenbelt, Theodora C. van Tilborg, et al. **Preimplantation Genetic Testing for Monogenic Kidney Disease: Developments in the Netherlands.** CJASN doi: 10.2215/CJN. 03550320. Visual Abstract by Edoar Lerma. MD. FASN

ADPKD PGT: The Netherlands experience

Preimplantation Genetic Testing for Monogenic Kidney Disease

Rozemarijn Snoek,¹ Marijn F. Stokman,¹ Klaske D. Lichtenbelt,¹ Theodora C. van Tilborg,² Cindy E. Simcox,² Aimée D.C. Paulussen,^{1,3} Jos C.M.F. Dreesen,³ Franka van Reekum,⁴ A. Titia Lely,⁵ Nine V.A.M. Knoers,^{1,6} Christine E.M. de Die-Smulders,³ and Albertien M. van Eerde¹

CJASN 15: 1279–1286, 2020. doi: <https://doi.org/10.2215/CJN.03550320>

Table 2. Referral indications on preimplantation genetic testing for monogenic kidney disease

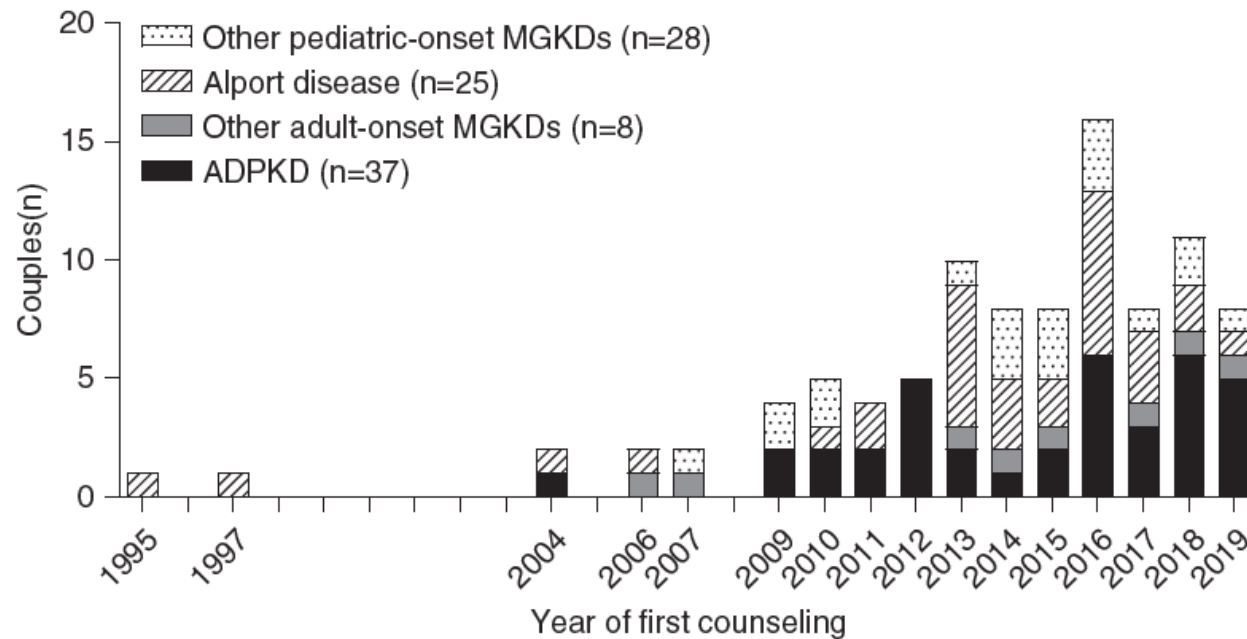
Disease	n (%)	Gene (n)
Autosomal dominant inheritance		
ADPKD ^a	37 (38)	PKD1 (35), PKD2 (2)
Brachio-oto-renal syndrome	5 (5)	EYA1 (5)
INF2-related FSGS ^a	3 (3)	INF2 (3)
Nail-patella syndrome ^a	3 (3)	LMX1B (3)
PAX2-related disease	2 (2)	PAX2 (2)
aHUS ^a	1 (1)	CFH (1)
ADTKD-HNF1B ^a	1 (1)	HNF1B (1)
Autosomal recessive inheritance		
ARPKD	9 (9)	PKHD1 (9)
Joubert syndrome	7 (7)	CEP290 (5), TCTN3 (1), C5ORF42 (1)
Bardet-Biedl syndrome	1 (1)	BBS7 (1)
Cystinosis	1 (1)	CTNS (1)
Nephrotic syndrome	1 (1)	COQ2 (1)
X-linked inheritance		
Alport syndrome	25 (26)	COL4A5 (25)
Nephrogenic diabetes insipidus	2 (2)	AVPR2 (2)
ADPKD, autosomal dominant polycystic kidney disease; aHUS, atypical hemolytic-uremic syndrome; ADTKD, autosomal dominant tubulointerstitial kidney disease; ARPKD, autosomal recessive polycystic kidney disease.		
^a Adult-onset disease.		

ADPKD PGT: The Netherlands experience

Preimplantation Genetic Testing for Monogenic Kidney Disease

Rozemarijn Snoek,¹ Marijn F. Stokman,¹ Klaske D. Lichtenbelt,¹ Theodora C. van Tilborg,² Cindy E. Simcox,² Aimée D.C. Paulussen,³ Jos C.M.F. Dreesen,³ Franka van Reekum,⁴ A. Titia Lely,⁵ Nine V.A.M. Knoers,^{1,6} Christine E.M. de Die-Smulders,³ and Albertien M. van Eerde¹

CJASN 15: 1279–1286, 2020. doi: <https://doi.org/10.2215/CJN.03550320>



PGT in Italy

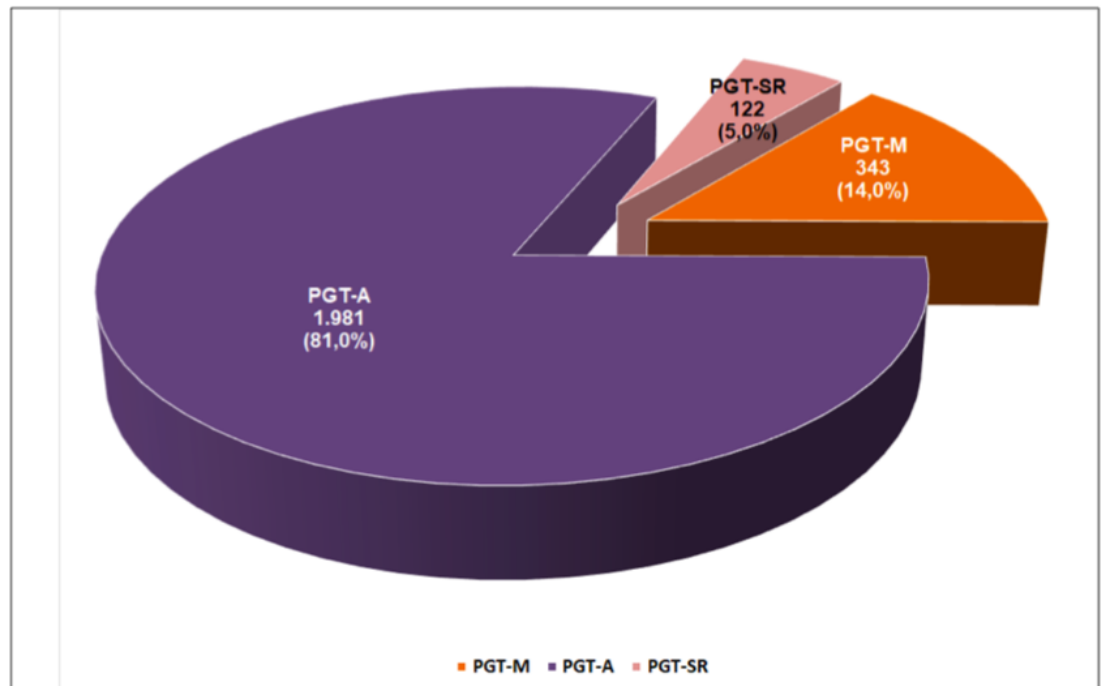


Figura 2.18: Distribuzione dei cicli di PMA con indagini genetiche effettuate nel 2018 secondo la tipologia di indagine eseguita (2.447 indagini genetiche).

Preimplantation genetic testing in Italy



Tabella 4.46: Distribuzione del numero di centri e del numero di cicli in cui sono state effettuate indagini genetiche secondo la tipologia di servizio del centro. Anno 2018

Tipologia del servizio	Centri che hanno effettuato almeno 1 ciclo con un'indagine genetica	Cicli in cui si prevede di effettuare indagini genetiche su embrioni a fresco	Cicli in cui sono state effettuate indagini genetiche su embrioni scongelati
Pubblico	6	101	19
Privato convenzionato	10	736	151
Privato	30	2.387	47
Totale	46	3.224	217

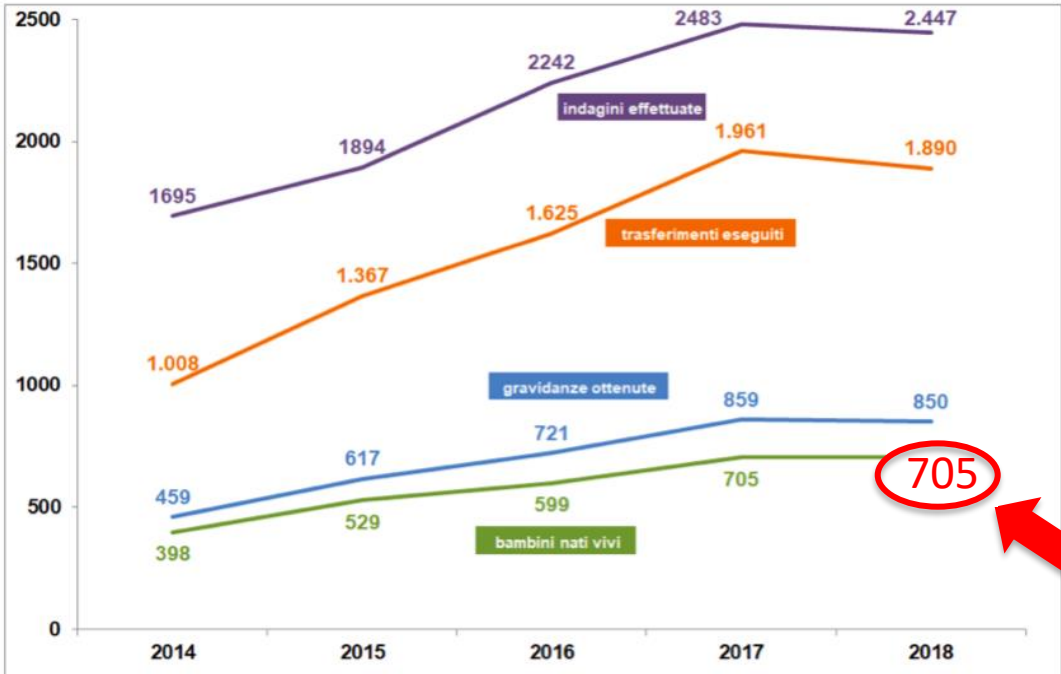


Figura 2.33: Distribuzione temporale dei risultati dei cicli di PMA di II e III livello in cui sono state effettuate indagini genetiche.

Fonte: ISS 2019

PGT in Italy



Registro Nazionale Procreazione Medicalmente Assistita

Centri in Italia

ISS : RPMA : Centri in Italia e Referenti Regionali

Regione:

Regione Campania

Centri selezionati 44

* visualizza la definizione di livello centro

Centro	Pr	Liv. *	Servizio	Scheda
Centro Chemis Iaccarino Via F. Caracciolo, 2 - 80122 - Napoli	NA	I	Privato	
Centro di Fecondazione Assistita Villa Bianca Via Bernardo Cavallino, 102 - 80128 - Napoli	NA	III	Privato	
Centro di PMA - Clinica Mediterranea Via Orazio, 2 - 80122 - Napoli	NA	III	Privato	
Centro di PMA - P.O. Santa Maria delle Grazie di Pozzuoli - ASL NA2 nord Via Domiziana - c/o Ospedale S. Maria delle Grazie - 80078 - Pozzuoli	NA	II	Pubblico	
Centro di PMA Dott. Sannino Ferdinando Via Viscardi, 47 - 80147 - Napoli	NA	I	Privato	
Centro di PMA per la Diagnosi e Terapia dell'Infertilità di Coppia - Dott. Sosa Fernandez Viale Puglia, 35/39 - 80053 - Castellammare di Stabia	NA	II	Privato	
Centro di Procreazione Medicalmente Assistita - Casa di Cura Ruesch Viale Maria Cristina di Savoia, 39 - 80122 - Napoli	NA	III	Privato	
Centro di Sterilità - Az. Univ. Policlinico - Università degli Studi di Napoli Federico II Via Pansini, 5 - 80131 - Napoli	NA	III	Pubblico	
Centro Fecondazione Assistita "Andrea Grimaldi" Via G. Marconi, 4/10 - 80046 - San Giorgio a Cremano	NA	II	Privato	
Centro Medico "Canero" Via Milano, 131 - 80145 - Napoli	NA	I	Privato	
Centro per lo Studio della Coppia Infertile	NA	I	Privato	

Selezionare una regione



Totale Centri nella regione: 44

<https://w3.iss.it/site/registropma/pub/centri/centripma.aspx>

PGT in Italy



Stato attuale del Centro: AUTORIZZATO

ANAGRAFICA DEL CENTRO

Le informazioni contenute in questa sezione sono controllate e confermate dalle Regioni di appartenenza dei centri. Dati aggiornati al 30/09/2021

Centro Provinciale per la Procreazione Medicalmente Assistita - Ospedale Alto Garda e Ledro

Tipo di Servizio e Livello: Pubblico, Livello III

Indirizzo: Via Capitelli, 48 - 38062 - Arco - TN

Telefono: 0464/582562

Fax: 0464/582769

Email: ama.luehwink@apss.tn.it

Responsabile del Centro: Dr. Ama Luehwink

DATI TECNICI

Le informazioni in questa sezione vengono fornite direttamente dai centri che hanno piena responsabilità di tali dichiarazioni. Dati revisionati il 19/05/2021

Tecniche applicate

IUI: Si ICSI: Si RVET: Si GIFT: No
Cicli con Donazione di Gameti: Si Attività di crioconservazione degli embrioni (FER)*: Si
Indagini Genetiche: PGD+PGS Attività di crioconservazione degli ovociti (FO)*: Si
Trattamento coppie sierodiscordanti per HIV: No Attività di crioconservazione degli spermatozoi*: Si
Altre Tecniche:
Social freezing
Medical freezing
Esterologa da donazione gameti centri esteri

Metodologie di prelievo chirurgico degli spermatozoi

MESA: Si TESA: Si MESE: Si TESE: Si PESA: Si
Altre Metodologie

* Le risposte "SI" alle attività di crioconservazione si riferisce a chi esegue queste tecniche nella sua pratica clinica di routine. Per legge tutti i centri di II e III Livello debbono dotarsi di attrezzature adeguate per applicare le migliori tecniche di crioconservazione e scongelamento dei gameti e di crioconservazione degli embrioni (linea guida 1 luglio 2015 "Crioconservazione dei gameti", accordo Stato-Regioni 15 marzo 2012)

PROFILO DEL CENTRO - Dati Attività 2018

Il responsabile attuale del Centro indicato nella sezione "Anagrafica" potrebbe non essere il responsabile dei dati di seguito riportati.

% Diagnosi di infertilità delle 459 coppie sottoposte a cicli a fresco (ICSI, FIVET, GIFT) Senza Donazione

Fattore tubarico	8,5 %	Fattore maschile	26,4 %
Ridotta riserva ovarica	11,3 %	Fattore maschile e femminile	27,7 %
Infertilità multipla femminile	9,6 %	Infertilità inspiegata	10,7 %
Infertilità endocrina/ovulatoria	2,0 %	Fattore genetico	0,4 %
Endometriosi	3,5 %	Poliboriovità	0,0 %

Cicli Senza Donazione di Gameti

IUI	187
ICSI	518
FIVET	0
FER	87
FO	4
Totale	796

Cicli con Donazione di Gameti

IUI (Donazione Seme)	0
ICSI / FIVET *	16
* (sono compresi i cicli di II e III Livello che hanno utilizzato una donazione di gameti, zigoti o embrioni)	
Totale	16

Cicli per età delle pazienti

	TOTALE	≤ 34	35 - 39	40 - 42	≥ 43
Totale cicli a fresco (Icsi, Fivet, Gift)	518	182	175	120	41
Totale cicli da scongelamento di embrioni (FER)	87	41	34	9	3
Totale cicli da scongelamento di ovociti (FO)	4	2	1	0	1

La sezione "Profilo del Centro" contiene l'attività svolta in termini di cicli eseguiti secondo le varie tecniche applicate e con la tipologia di pazienti trattati con cicli a fresco, in base alle diagnosi di infertilità e alla loro età. Queste informazioni si riferiscono agli ultimi dati disponibili (come indicato nella stessa sezione), e fanno riferimento all'attività svolta dal

REGIONE TRENINO ALTO ADIGE

PGT in Italy



Stato attuale del Centro: AUTORIZZATO

ANAGRAFICA DEL CENTRO

Le informazioni contenute in questa sezione sono controllate e confermate dalle Regioni di appartenenza dei centri. Dati aggiornati al 30/09/2021

Centro Provinciale per la Procreazione Medicalmente Assistita - Ospedale Alto Garda e Ledro

REG

Tipo di Servizio e Livello: Pubblici

Indirizzo: Via Capitelli, 48 - 38062

Telefono: 0464/582562

Email: amo.ledro@apss.in.it

Responsabile del Centro: Dr. Am

DATI TECNICI

Le informazioni in questa sezione vengono fornite direttamente dai centri che hanno piena responsabilità di tali dichiarazioni. Dati revisionati il 19/05/2021

Tecniche applicate

IUI: Sì

ICSI: Sì

FIVET: Sì

GIFT: No

Cicli con Donazione di Gameti: Sì

Indagini Genetiche: PGD+PGS

Trattamento coppie sierodiscordanti per HIV: No

Altre Tecniche

Social freezing

Medical freezing

Eterologa da donazione gameti centri esteri

Attività di crioconservazione degli embrioni (FER)*: Sì

Attività di crioconservazione degli ovociti (FO)*: Sì

Attività di crioconservazione degli spermatozoi*: Sì

Metodologie di prelievo chirurgico degli spermatozoi

MESA: Sì

TESA: Sì

MESE: Sì

TESE: Sì

PESA: Sì

Altre Metodologie

Tecniche applicate

IUI: Sì

Cicli con Donazione

Indagini Genetiche: PGD+PGS

Trattamento coppie sierodiscordanti

Altre Tecniche

Social freezing

Medical freezing

Eterologa da donazione gameti

Metodologie di prelievo chir.

MESA: Sì

TES

Altre Metodologie

* La risposta "Sì" alle attività di crioconservazione attesta l'adeguatezza per applicare le migliori tecniche di crioconservazione e scongelamento dei gameti e di crioconservazione degli embrioni (linee guida 1 luglio 2015 "Crioconservazione dei gameti", accordo Stato/Regioni 15 marzo 2012)

Il responsabile attuale del Centro indica:

% Diagnosi di infertilità delle

Fattore tubarico

Ridotta riserva ovarica

Infertilità multipla femminile

Infertilità endocrina/ovulatoria

Endometriosi

Cicli Senza Donazione di Gameti

IUI

ICSI

FIVET

FER

FO

Totale

187
518
0
87
4
796

Cicli con Donazione di Gameti

IUI (Donazione Seme)

ICSI / FIVET *

* (sono compresi i cicli di I e II Livello che hanno utilizzato una donazione di gameti, zigoti o embrioni)

Totale

0
16
16

Cicli per età delle pazienti

TOTALE	≤ 34	35 - 39	40 - 42	≥ 43
518	182	175	120	41
87	41	34	9	3
4	2	1	0	1

Totale cicli a fresco (Icsi, Fivet, Gift)

Totale cicli da scongelamento di embrioni (FER)

Totale cicli da scongelamento di ovociti (FO)

La sezione "Profilo del Centro" contiene l'attività svolta in termini di cicli eseguiti secondo le varie tecniche applicate e con la tipologia di pazienti trattati con cicli a fresco, in base alla diagnosi di infertilità e alla loro età. Queste informazioni si riferiscono agli ultimi dati disponibili (come indicato nella stessa sezione), e fanno riferimento all'attività svolta dal

PGT BRESCIA-PADOVA

2016-2019

- ADPKD patients: 2 females e 13 males
- **only *PKD1* pathogenic variants**
- *All familial cases*

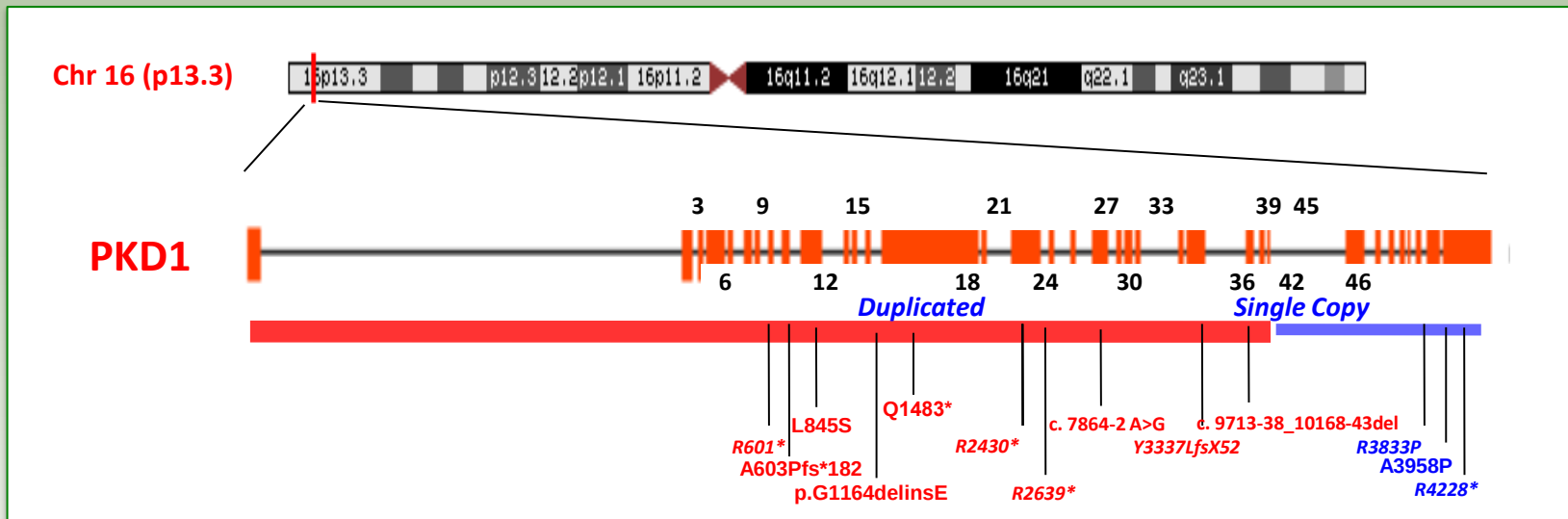


- 1) c.11498G>C (p.R3833P)
- 2) c. 7288C>T (p.R2430*)
- 3) c. 1803delG (p.R601*)
- 4) c. 12682C>T (p.R4228*)
- 5) c. 10009_10010insT (p.Tyr3337LeufsX52)
- 6) c. 7915C>T (p.R2639*)
- 7) c. 4447 C>T (p.G1483*)
- 8) c. 7864-2 A>G

- 9) c. 7288C>T (p.R2430*)
- 10) c. 9713-38_10168-43del
- 11) c. 3491_3492delinsAA (p.Gly1164delinsGlu)
- 12) c. 1803delG (p.A603Pfs*182)
- 13) c. 2534 T>C (p. L845S)
- 14) c. 11872 G>C (p. A3958P)
- 15) c. 4447C>T p.(Gln1483*)

PGT BRESCIA-PADOVA

2016-2019



Posizione delle mutazioni identificate nei soggetti affetti rispetto alla regione duplicata di PKD1

- **Probabilità di riuscita della PGD: 54% per singolo embrione trasferito**
- **L'accuratezza della PGD è superiore al 98%.**
- **In caso di gravidanza si raccomanda una diagnosi prenatale per confermare la diagnosi genetica preimpianto**

Preimplantation genetic testing in Italy



PGT UNIT

DR.SSA DANIELA ZUCCARELLO

ambulatorio.genetica@aopd.veneto.it

*Azienda Ospedale Università di Padova,
UOC di Genetica ed Epid. Clinica*

CENTRI PGT IN SSN

Ospedale di Arco (TN) Centro PMA

Dr Arne Luehvink

Ospedale di Ferrara

Centro PMA

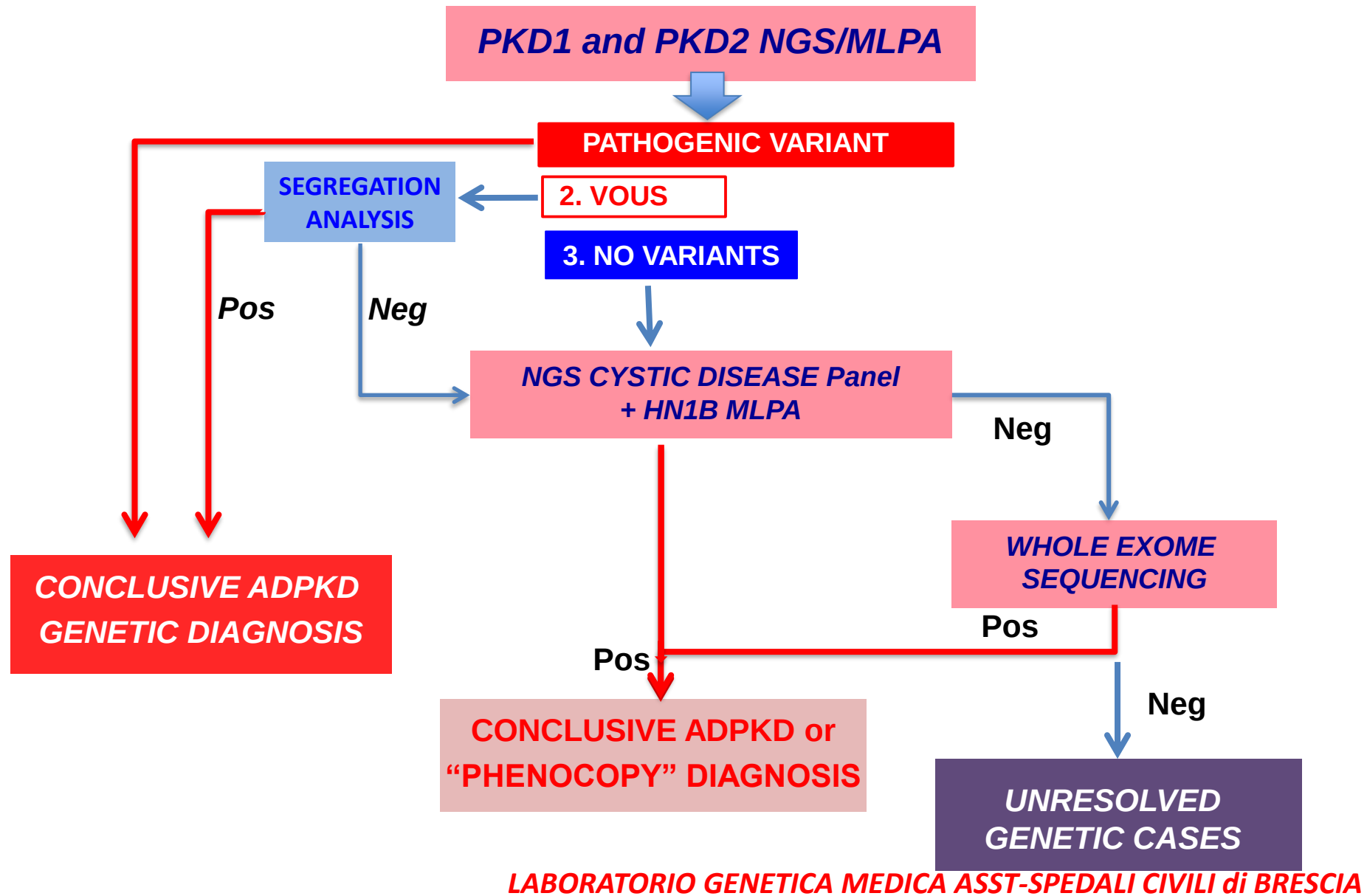
Dr A Gallinelli Dr F Capodanno

Azienda Ospedaliera Universitaria Senese

Genetica medica

Prof Alessandra Renieri

MOLECULAR DIAGNOSTIC WORKFLOW IN “ADPKD” PATIENTS



Pannelli malattie genetiche renali-Brescia

Ciliopathies, cystic kidney disease and differential diagnosis

MALATTIE CISTICHE RENALI e CILIOPATIE con coinvolgimento renale

Sono compresi nel pannello la maggior parte delle patologie che possono presentare fenotipo cistico renale

AHI1 ALG8 ALG9 ALMS1 ANKS6 ARL13B ARL3 ARL6 ARMC9 ATXN10 B9D1 B9D2 BBIP1 BBS1 BBS2 BBS4 BBS5 BBS7 BBS10 BBS12 BBS9 BICC1 C5orf42 C8orf37 C2CD3 CC2D2A CCDC28B CCND1 CELSR2 CEP41 CEP55 CEP104 CEP120 CEP164 CEP290 COL4A1 COL4A3 COL4A4 COL4A5 CRB2 CSPP1 DDX59 DHCR7 DNAJB11 DYNC2H1 DYNC2LI1 DZIP1L ETFA EYA1 FLCN EXOC4 GANAB GLI3 GLIS2 GPC3 HNF1B HNF4A HSD17B4 IFT43 IFT122 IFT140 IFT172 IFT27 IFT43 IFT80 IFT81 IFT74 IFT172INPP5E INTU INVS IQCB1 KAT6B KIAA0753 KIAA0556 KIAA0586 KIF7 KIF14 LRP5 LZTFL1 MKKS MKS1 NEK1 NEK8 NPHP1 NPHP3 NPHP4 NRIP1 OFD1 PDE6D PDPR PIBF1 PMM2 PKD2 PKHD1 PRKCSH REN RPGRIP1L SCAPER SCLT1 SDCCAG8 SEC61A1 SEC63 SLC41A1 SLSN3 SUFU TBC1D32 TCTN1 TCTN2 TCTN3 TCTEX1D2 TFAP2A TMEM67 TMEM107 TMEM138 TMEM216 TMEM231 TMEM237 TRAF3IP1 TRIM32 TSC1 TSC2 TTC21B TTC8 TXNDC15 UMOD VHL WDPCP WDR19 WDR60 XPNPEP3 ZNF423

- RENE POLICISTICO AUTOSOMICO DOMINANTE (ADPKD)

PKD1, PKD2, ALG8, ALG9, DNAJB11, GANAB, SEC63, SEC61A1, PARN, PRKCSH, PKHD1

- Nefronoftisi (compresi i geni associati a Senior-Loken syndrome)

AHI1, ANKS6 (NPHP16), ATXN10, BBS4, BBS5, BBS7, BBS9, C8orf37 (BBS21), CC2D2A, CCDC28B (BBS1), CEP83 (NPHP18) CEP164 (NPHP15), CEP290 (NPHP6), DCDC2 (NPHP19), GLIS2 (NPHP7) IFT27, IFT43, IFT74, IFT140, IFT172, INVS (NPHP2), IQCB1 (NPHP5), LZTFL1 (BBS17), MAPKBP1 (NPHP10), MKKS (BBS6), NEK8 (NPHP9) NPHP1, NPHP3, NPHP4, RPGRIP1L (NPHP8), SDCCAG8 (BBS16), SLC41A1, TMEM138, TMEM216 TMEM67 (NPHP11), TRAF3IP1 TRIM32 (BBS11), TTC21B (NPHP12), TTC8 (BBS8), WDPCP (BBS15), WDR19 (NPHP13), WDR35, XPNPEP3, ZNF423 (NPHP14)

- Sclerosi Tuberosa

TSC1 TSC2

- Sindrome di Von Hippel Lindau

CCND1 VHL

Patologia malformativa renale

CAKUT

ACE AGT, ACTG1, AGTR1, ARL6, BBIP1, BBS1 BBS2 BBS4 BBS5 BBS7 BBS9 BBS10 BBS12, BICC1, BMP7, CCDC28B, CDC5L, CEP290, CEP55, CHD7, C8orf37, CTU2, DHCR7, DSTYK, EYA1, FGF20, FOXC1, FOXP, FRAS1, FREM1, FREM2, GATA3, GDNF, GLI3 GPC3 GRIP1, GREB1L, GREM1 HNF1B, IFT172, IFT27, IFT74, ITGA8, KCTD1 LCAT LHX1, LZTFL1, MKKS, MKS1, MRPS7, NPHP1, NRIP1, OSR1, PAX2, PAX8, PBX1, POU6F2, RET, ROBO2, SALL1, SALL4 SARS2, SCAPER, SDCCAG8, SEMA3E (CHARGE), SIX1, SIX5, SLIT2, SOX17, TBC1D1, TBX18, TFAP2A TRAP1 TRIM32, TTC8, UPK3A, WDPCP, WT1, WNT4, WNT5A

Tubular dysgenesis

ACE AGT AGTR1 LCAT MRPS7 REN SARS2

Wilms tumor

POU6F2 WT1

Glomerular diseases

Glomerulosclerosi Focale Segmentale (FSGS) e Sindrome Nefrosica Steroide-Resistente (SNSR)

ACTN4 ALG1 ANLN, APOL1 ARHGDI1 ARHGAP24 ARL6 APOL1 AVIL BBIP1 BBS1 BBS10 BBS12 BBS2 BBS4 BBS5 BBS7 BBS9 C3, CFB, CFI CD46 (MCP) C8orf37 CCDC28B CD2AP CFH, CLCN5, COL4A3 COL4A4 COL4A5, COQ2, COQ6, COQ8B (ADCK4) CRB2, CTNS, DGKE EMP2 FAH FN1 GLA, GSN, INF2, KANK1, KANK2, KANK4, KIAA1291, KIRREL1 (NEPH1), ITGA3, LAGE3, LAMB2, LMX1B, LZTFL1, LYZ, MAGI2 MKKS MYO1E, MYH9, NOS1AP, NPHS1 NPHS2 NUP107 NUP133 NUP160 NUP205 NUP85 NUP93 OSGEP PAX2, PDSS2, PLCE1 PTPRO, SCARB2, SGPL1 SLC37A4 SMARCA1, SYNPO, TBC1D8B, THBD, TP53RK, TPRKB, TRIM32 TRPC6 TTC8 TTC21B WDR73 WDPCP WT1

Glomerulonefrite membranoproliferativa (GNMP) e Glomerulopatia a depositi di C3

CFH, CD46 (MCP), C3, CFB, CFI, THBD, DGKE

Alport syndrome

COL4A3 COL4A4 COL4A5

Fabry disease

GLA

Tubulointerstitial diseases

Malattie tubulointerstiziali Autosomiche Dominante (ADTKD) e nefropatie in diagnosi differenziale (Attenzione MUC1 non incluso)

UMOD, REN, HNF1B, PARN, SEC61A1, APOA1, DNAJB11, CLCN5, OCRL, COL4A3, COL4A4, COL4A5, FAN1

Tubular diseases

Tubulopatie (patologie con alterazione della funzione del tubulo, include tutti i sottogruppi sottoelencati):

ADCY10, AGXT APRT, CASR CLCNKB CLCN5 CLDN14, CLDN16 CLDN19 CYP24A1, FAH, FAM20A GRHPR XDH HGD HNF4A HOGA1 HPRT1 MOCOS OCRL SLC12A1 SLC22A12 SLC2A9 SLC3A1 SLC7A9 SLC34A1 SLC34A3 SLC4A1 SLC9A3R1 BSND CLCNKA KCNJ1 MAGED2 SLC12A3 EHHADH GATM HOGA1 ATP6V0A4 ATP6V1B1 BCS1L CA2 CLDN16 FOXI1 OCRL SLC4A1 SLC4A4 VDR VIPAS39 VPS33B OCRL SCNN1A SCNN1B SCNN1G AQP2 AVP AVPR2

- Bartter - Gitelman syndrome-Renal tubular defect

BSND CASR CLCNKA CLCNKB KCNJ1 MAGED2 SLC12A1 SLC12A3 EHHADH GATM

- Hyperoxaluria

AGXT GRHPR HOGA1

- Renal tubular acidosis

ATP6V0A4 ATP6V1B1 BCS1L CA2 CLDN16 FOXI1 OCRL SLC4A1 SLC4A4 VIPAS39 VPS33B

- Dent disease

CLCN5 OCRL

- Nephrocalcinosis nephrolithiasis

ADCY10, AGXT APRT, CASR CLCNKB, CLCN5 CLDN14 CLDN16 CLDN19 CYP24A1 FAH FAM20A GRHPR HGD HNF4A, HOGA1 HPRT1, KCNJ1, MOCOS OCRL SLC12A1, SLC22A12 SLC2A9 SLC3A1 SLC7A9, SLC34A1, SLC34A3, SLC4A1, SLC9A3R1, XDH VDR

- Diabetes insipidus

AQP2 AVP AVPR2

- Liddle syndrome

SCNN1A SCNN1B SCNN1G

Take home messages

- Increasing in referrals for adult-onset monogenic kidney disease
- Increasing technical possibilities in genetic testing *Next-generation sequencing (NGS) has revolutionized genetic diagnostics*
- All patients with ADPKD who might consider having children *should be counseled about family planning and reproductive options, including PGT and available genetic services.*
- *Genetics becomes increasingly important for proper clinical management and prognostic issues*
- *Need of personalized and multidisciplinary approach to disease management*

BRESCIA NEPHROGENETIC CLINIC



**PROF.
FRANCESCO
SCOLARI**



C. IZZI



L. ECONIMO



R. CORTINOVIS



L. ZENI



C. DORDONI

**U.O Nefrologia e Dialisi
ASST-Spedali Civili Brescia**



G. SAVOLDI



C. MAZZA

*Laboratorio di Genetica Medica
ASST-Spedali Civili Brescia*

