Undiagnosed diseases program in Nijmegen, the Netherlands

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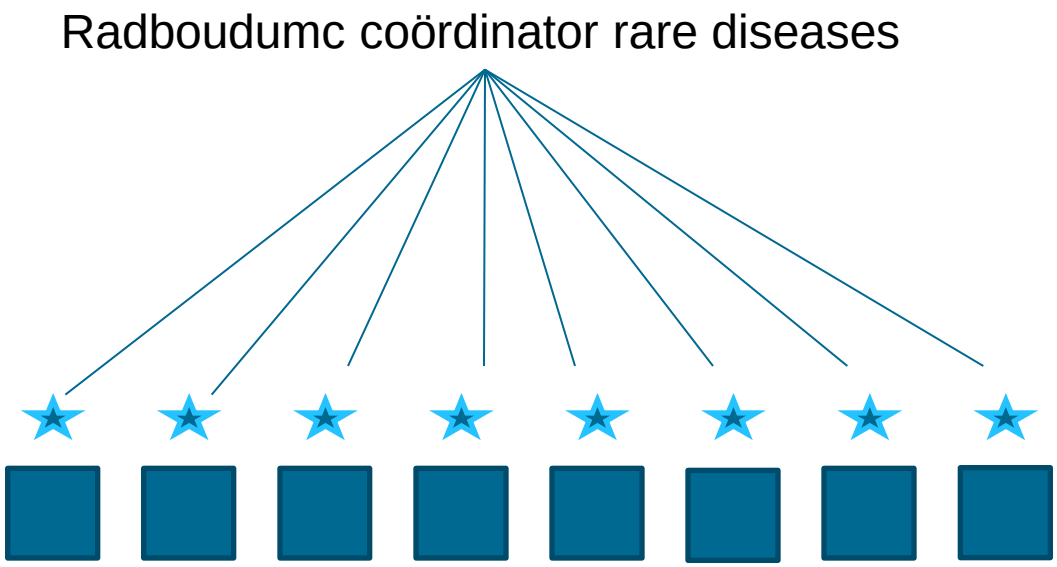
Human Genetics Nijmegen

Radboudumc

National plan rare diseases

- Presented 10-10-13 to the government
- 14/15-11-13: national conference on implementation of the plan
- No specific undiagnosed diseases plan; focus on early diagnosis and designation of centres of expertise

Rare diseases care in Radboudumc

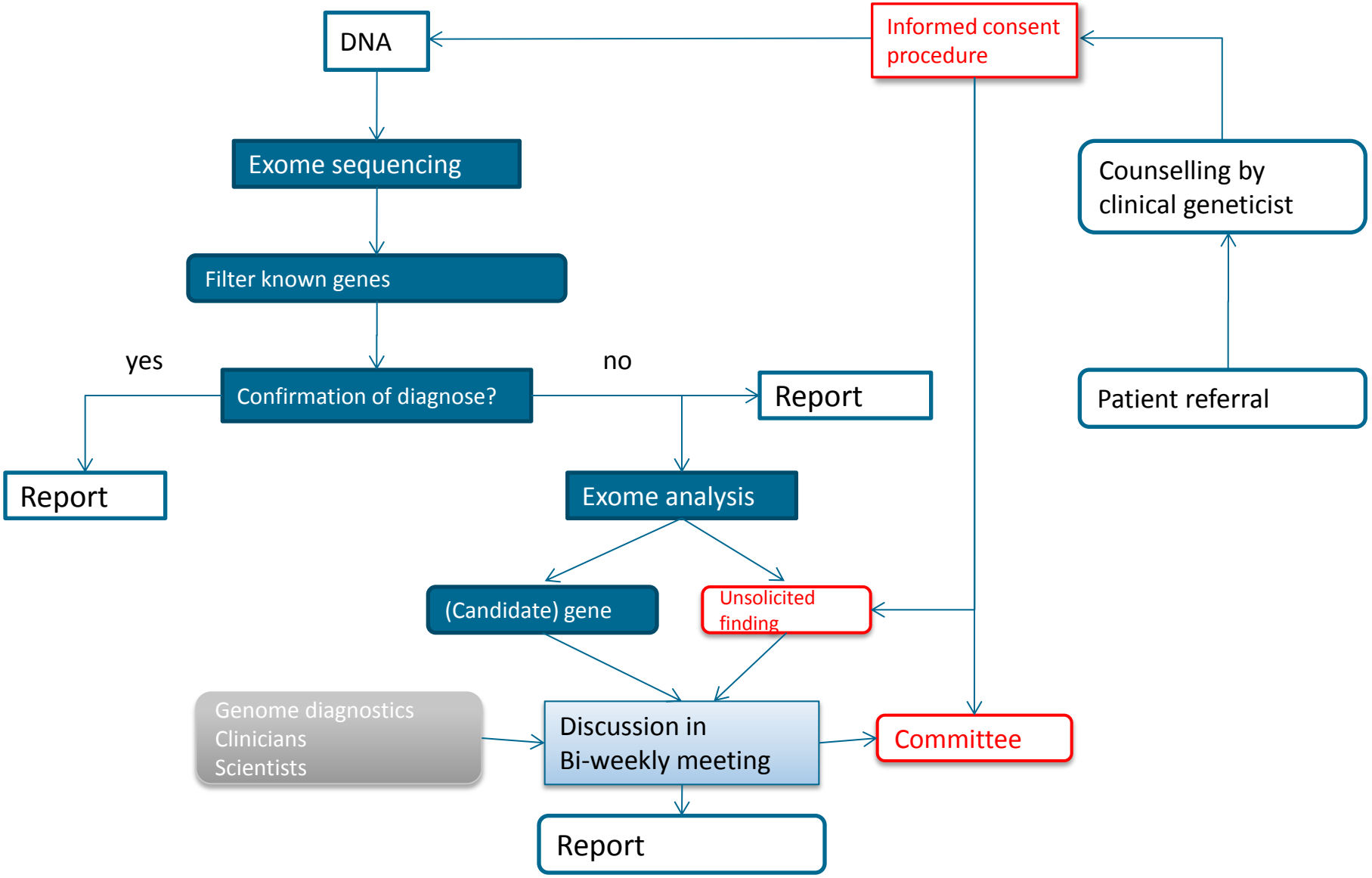


Diagnostic whole exome sequencing

‘All’ coding sequences of a human genome (>200,000 exons), sequenced and analyzed in **one** experiment

- Higher chance of finding the underlying genetic cause
- Compared to genome sequencing; less un-interpretive data
- Chance for unsolicited findings; reduced by a first step of filtering

WES workflow



Heterogeneous disease; gene package

- Movement disorders ~150 genes
- Hereditary blindness ~150 genes
- Hereditary deafness ~100 genes
- OXPHOS disorders ~200 genes
- Oncogenetics ~100 genes

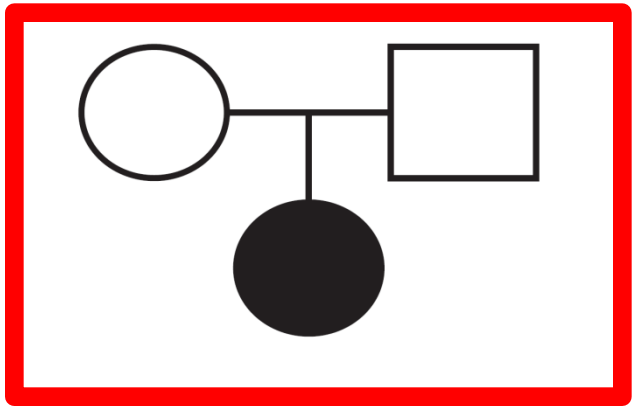
Diagnostic yield

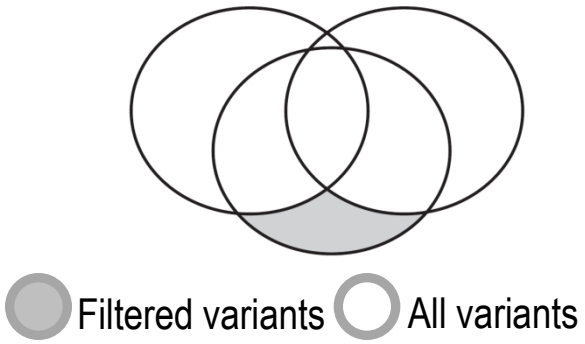
Package	Blindness	Deafness	Movement	OXPHOS	Oncogenetics
# pts	29	51	51	47	48
sequenced	25	33	38	43	35
analyzed	25	28	35	40	32
Causal mutations*	11	5	7	9	1
Diagnostic yield	44%	18%	20%	23%	2%

* Deleterious mutations or known pathogenic mutations

Total diagnostic yield : ***20-25%***

De novo strategy in ID patients

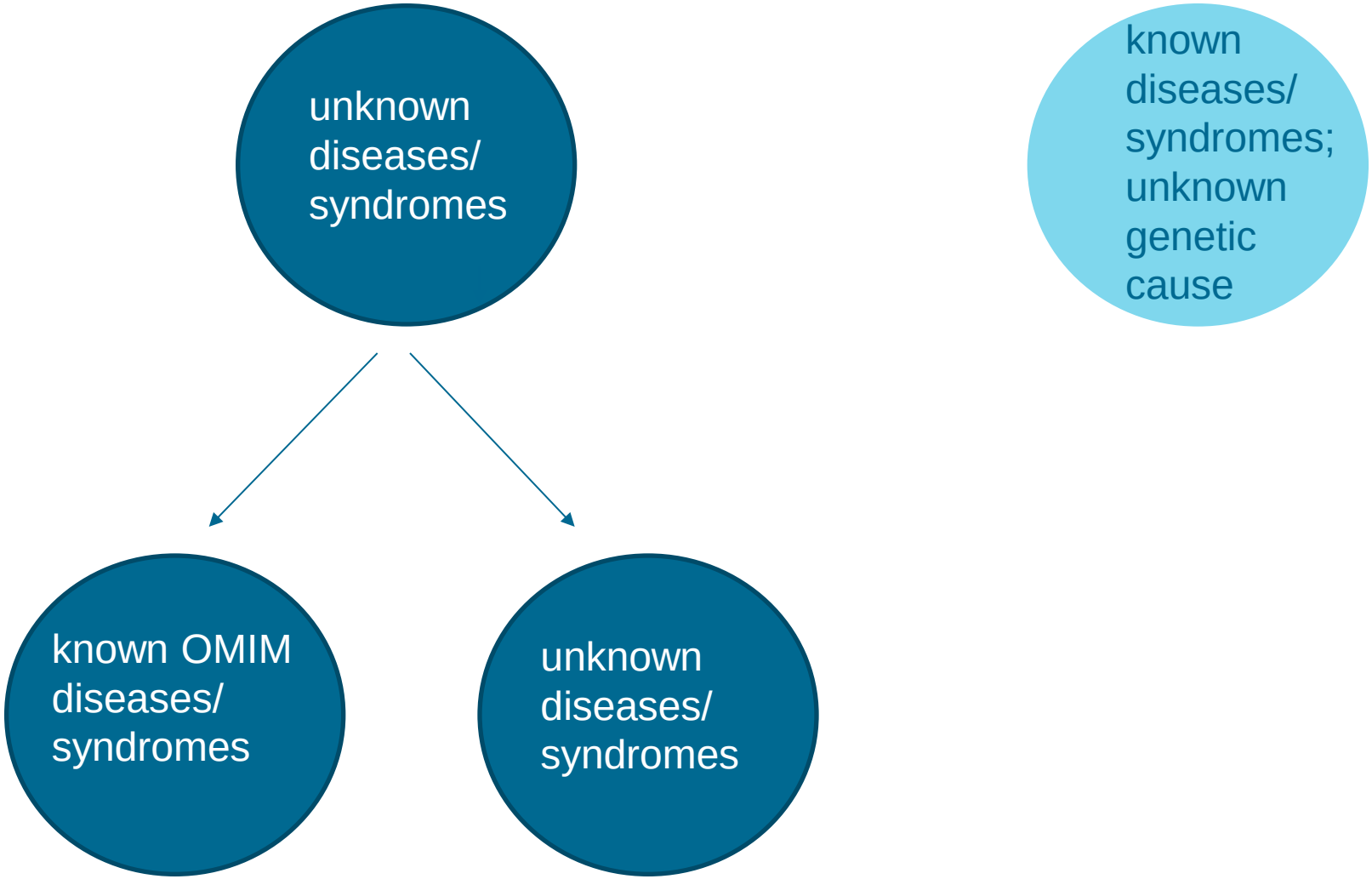




Diagnosis based on	*Number of patients*
Known ID genes	10
Known X-linked genes	3
Novel ID genes	3
Candidate ID genes	19*
Total	***16-35%***

**Of note, based on experience with testing for mutations in candidate genes it may be expected that at least 11 to 13 of these 19 genes will be true ID genes.*

Undiagnosed diseases without ID



Undiagnosed diseases without ID

collaboration with department of pediatrics, neurology and immunology/internal medicine

recruitment of patients with multi-systemic disorders/problems

with/without family history

selection of groups of patients with more or less the same problems if possible

Whole exome sequencing

- Diagnostic approach
- Analysis of “OMIM gene package” (2661 genes; 1/7 of all human genes)
- No family history: trio analysis for a *de novo* mutation analysis
- Sample collection in Radboudumc biobank
- Discussion of datacollection is ongoing:
  - Minimal dataset?
  - Clinical of genotype?

Undiagnosed diseases with ID

- Multidisciplinary approach
  - New patients with ID seen by clinical geneticist, pediatrician and pediatric neurologist after referral from general practioner or local pediatrician
  - If applicable, WES or WGS will be performed first
  - Management plan for parents
  - (back) referral to local pediatrician

Future plans

- Focus on early detection: genomics first
- Introducing “best practise” multidisciplinary approach
- Expanding field of referrals, involving general practioners
- International datacollection/registry