Ethical considerations related to PM clinical trials involving genome analysis

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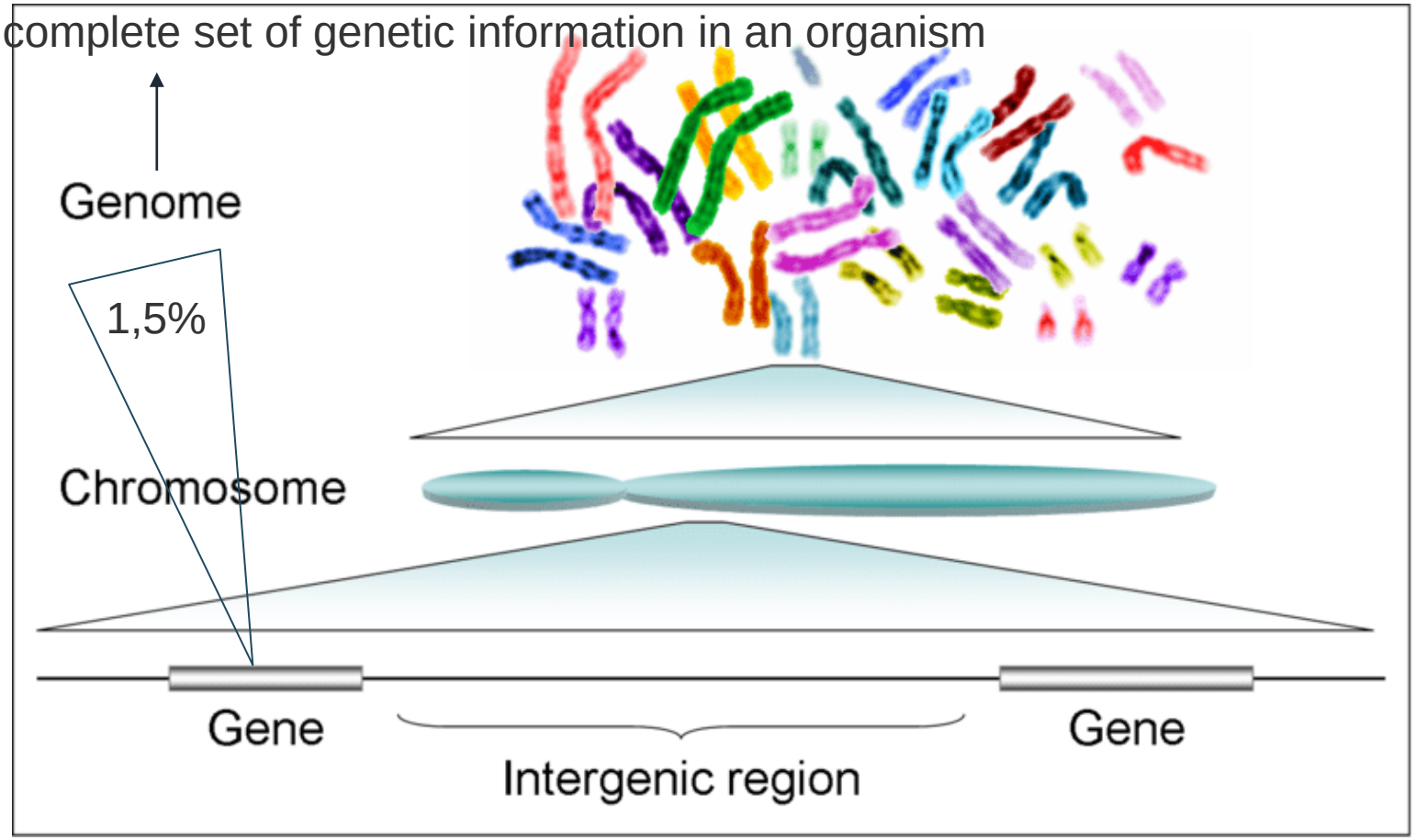
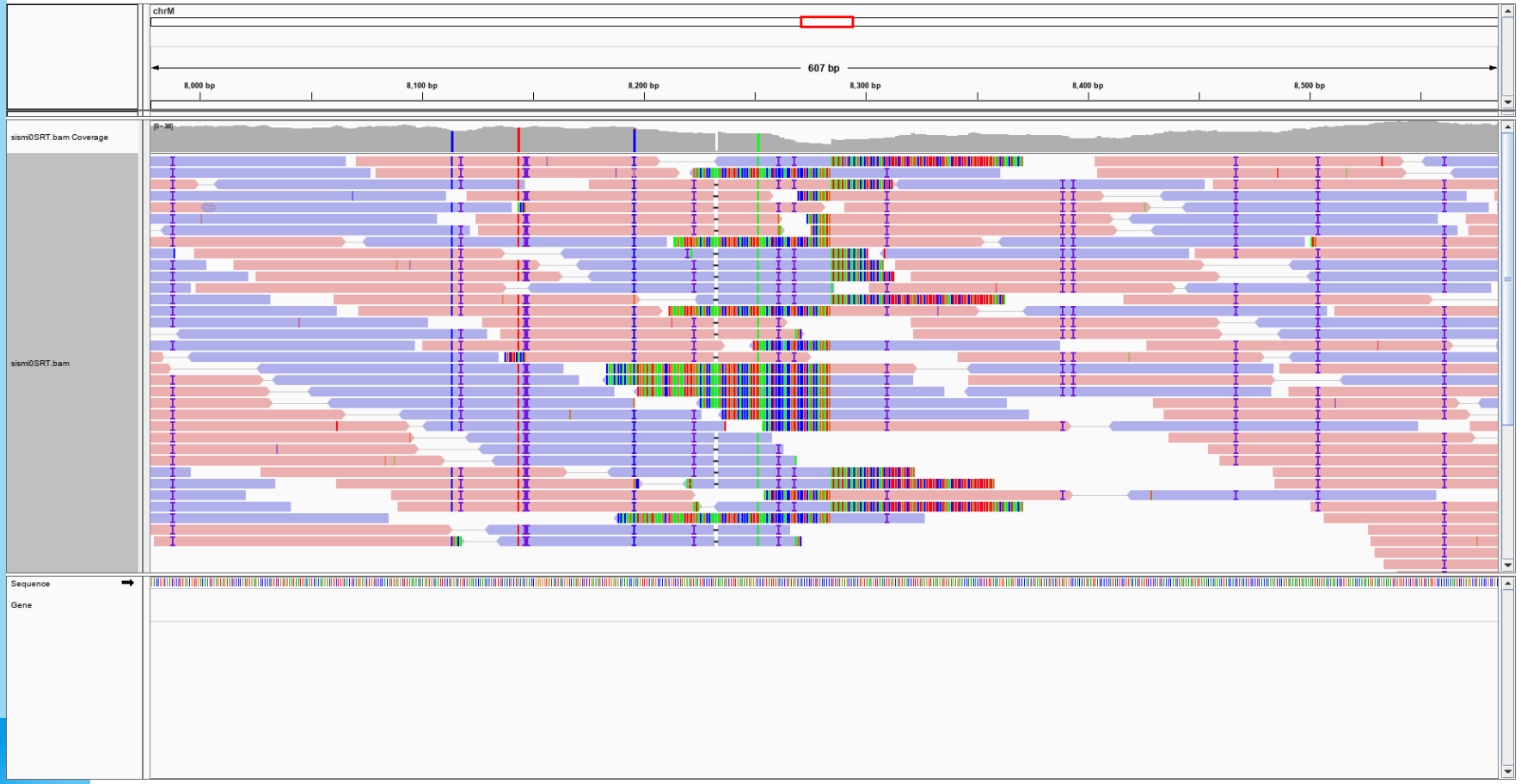
What is genome sequencing?

The complete set of genetic information in an organism

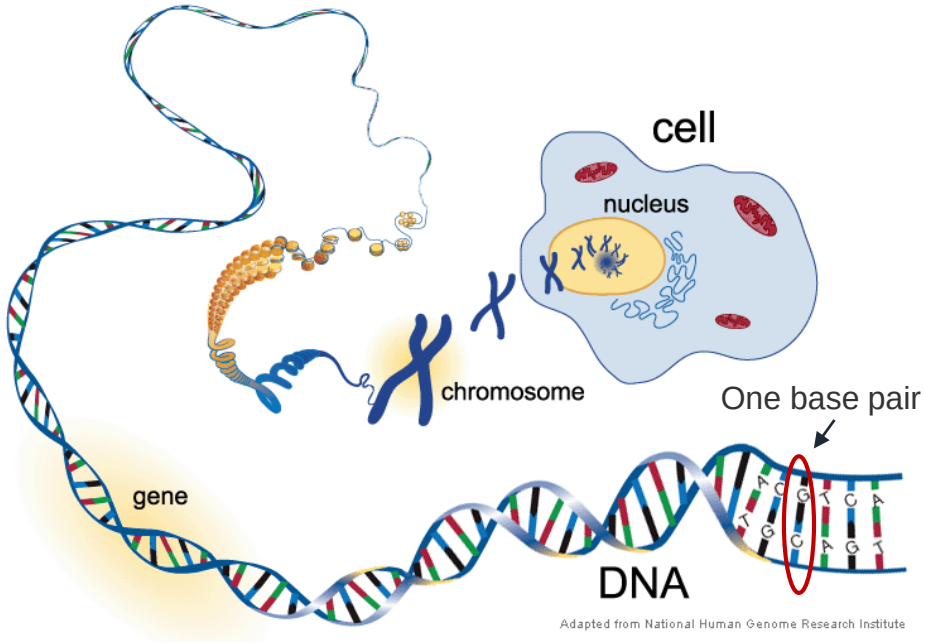


Homo sapiens has around 21,000 genes

Genome sequencing



Genetic variation



- The human genome consists of around 3 billion base pairs
- Genetic variants are deviations from the ”standard” (reference) genome
- Each human has around 20 millioner (0.6% of the genome) genetic variants

From ”Three Identical Strangers”

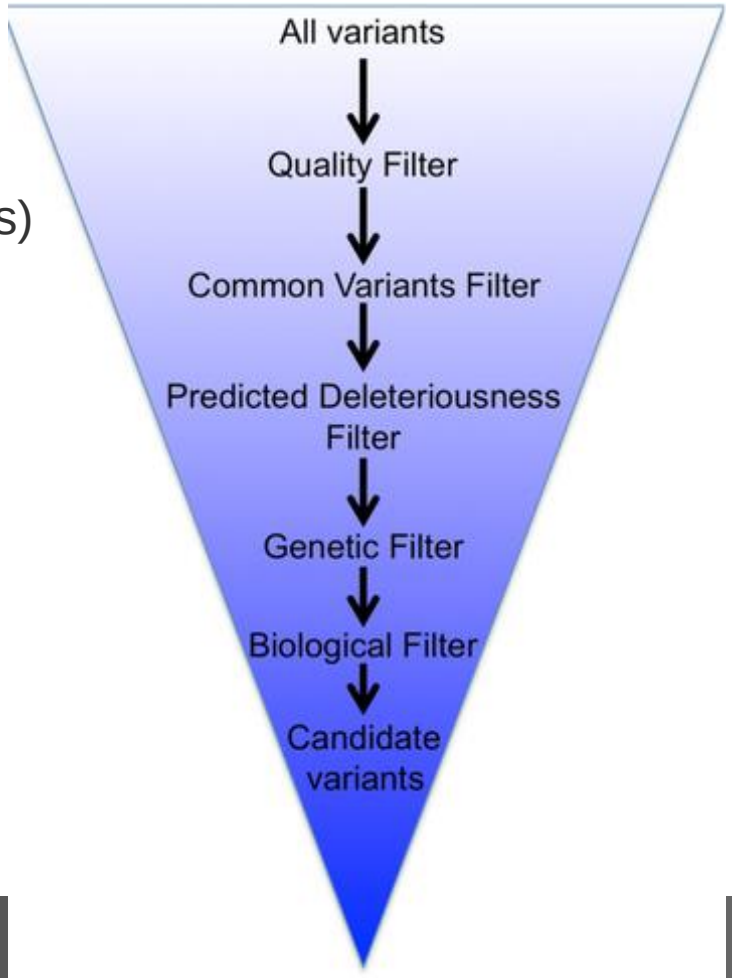
Filtering of genome data

Selection of genes (e.g. known disease-associated genes, cancer genes)

> 1% of the reference sequence

Effect on protein

Inheritance



What is a secondary (incidental) finding?

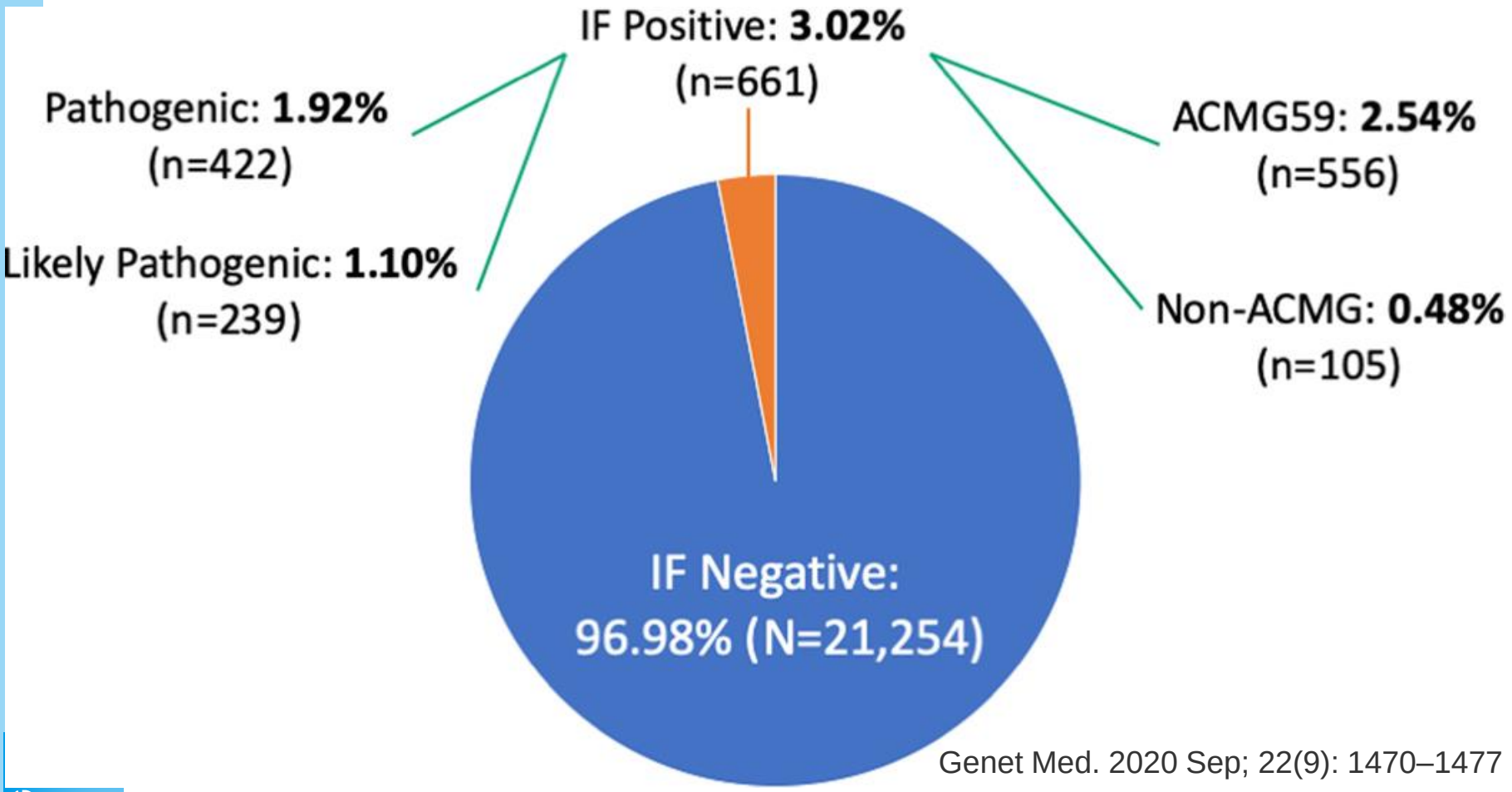
Important health-related incidental findings are findings identified in a health research project or health data research project that are unrelated to the project's purpose, revealing that the research participant or health data research participant (see section 7) unexpectedly suffers from or with certainty or a high degree of probability is predisposed to a life-threatening or clearly serious disease that can be treated, prevented or alleviated.

From NVK's guideline

ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

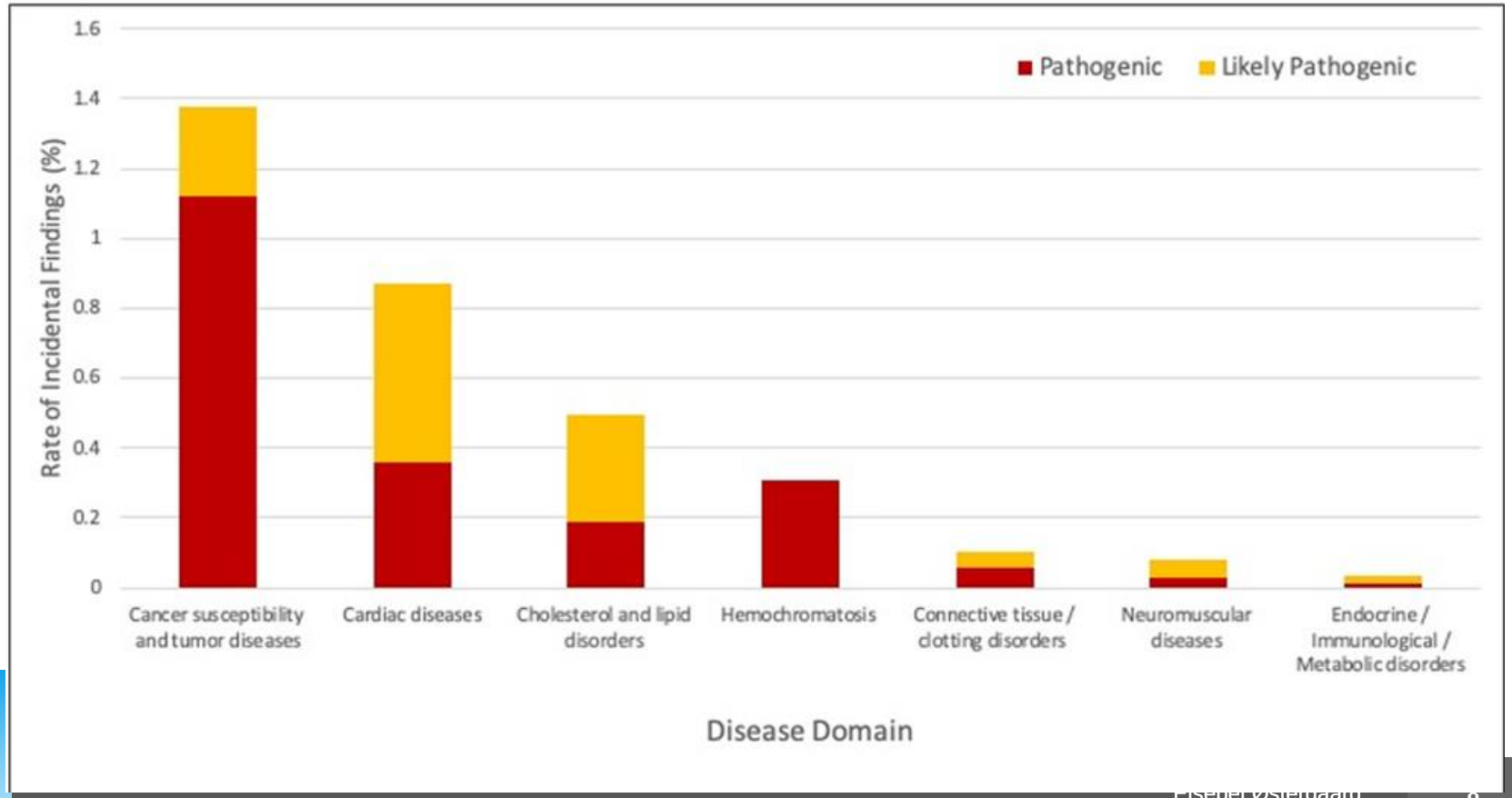
ACMG 59 Genes List | NIGMS Repository | Browse The Collection (coriell.org)

Frequency of secondary finding



Genet Med. 2020 Sep; 22(9): 1470–1477

Secondary findings according to disease areas



NATIONAL COMMITTEE ON HEALTH RESEARCH ETHICS

Guidelines on Genomics Research and Research in Sensitive Bioinformatics Data

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Methods within extensive mapping of the human genome

The list is annexed to the Guidelines on research projects involving extensive mapping of the human genome of the National Committee on Health Research Ethics.

- Whole genome sequencing (WGS)
- Whole exome sequencing (WES)
- Total RNA sequencing, e.g. sequencing of RNA from benign human tumours
- Genome-wide association studies (GWAS) with mapping of rare variants of potential predictive value to the research participants (e.g. the original version of Infinium Global screening array)
- Epigenetic studies based on NGS methods with DNA sequencing of a large number of regions in the human genome

Methods that are not extensive mapping of the human genome:

- Targeted sequencing, by which the sequencing targets a limited number of defined genes
- Genome-wide association studies (GWAS) with SNP arrays with mapping of frequent variants
- Epigenetic studies involving analysis not resulting in extensive sequencing data, e.g. the use of methylation assay not resulting in extensive sequencing data
- Genome-wide association studies (GWAS) with SNP arrays with mapping of frequent variants

The protocol should contain information about:

- Which region of the genome the project will be studying (gene panels, exomes, the whole genome, the epigenome, RNA).
- Which types of sequences the project intends to study (rare or common variants, structural variants, etc.).
- Which sequencing platform or high-density arrays the project intends to use.
- Which bioinformatic tools the project intends to use, e.g., variant calling, annotation and validation.
- Which sequencing depth the project intends to use.
- How the project intends to store raw data, where and for how long.
- An assessment of the estimated frequency of important health-related incidental findings along with reasons.

4.1. Committee of experts for assessment of incidental findings

In research projects involving a high risk of making important health-related incidental findings, the investigator or the health data investigator must describe their reasoned considerations about the likelihood of making important health-related incidental findings. See section 4(3) of the Executive Order on the Return of Findings.

The project must also describe the composition of the committee of experts that must be established if important health-related incidental findings are identified as well as procedures for how members to the committee of experts are appointed. See sections 5 and 6 of the Executive Order on the Return of Findings. The protocol could also describe the collaboration with a clinical genetics department in relation to the return of important health-related incidental findings.

The committee of experts must consist of a healthcare professional authorised in the studied disease area and must additionally consist of members possessing the necessary expertise to assess if the criteria for returning findings are met, cf. section 5 of the Executive Order on the Return of Findings. Read more about these criteria under 5.2 below.

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5.3. Return of important health-related incidental findings

The investigator or health data investigator may return important health-related incidental findings to the research participant or the health data research participant if there is certainty or a high degree of probability that the person concerned is predisposed to a life-threatening or clearly serious disease and the return of the information is necessary to protect the vital interests of the research participant or health data research participant.

The committee of experts must assess:

1) if the disease or disposition to disease can be significantly prevented, treated or alleviated

2) if the disease or disposition to disease is of major importance to the research participant or health data research participant

3) the clinical validity of the finding, and

4) if the method used to identify the finding is reliable.

The assessment of whether a finding should be returned is carried out jointly with the committee of experts or the clinical genetics department of a hospital. However, it is the investigator or health data investigator who ultimately decides if a finding should be returned to the participant.

KLINISK GENETISK KLINIK

Analyser

Enheder og laboratorier

Forskning og uddannelse

Henvisninger

Kontakt Klinisk Genetisk Klinik

Om klinikken

Undersøgelse og behandling

Klinisk etisk komite for genomanalyser

Formål

Formålet med komiteens arbejde er at sikre korrekt håndtering af helbredsmæssige fund, herunder sekundære fund, i forbindelse med diagnostiske analyser og videnskabelige projekter der er omfattet af NVKs "Vejledning vedr. genomforsøg".

Ved behov for vurdering af en variant påvist ifm et en diagnostisk analyse eller genomforsøg kontaktes komiteen, som foretager en vurdering af varianten.

Ved genomforsøg vurderes om varianten opfylder de fem kriterier for tilbagemelding i NVKs "Vejledning vedr. genomforsøg", og om fundet af varianten har en sådan betydning for forsøgspersonen at der skal ske en tilbagemelding.
Komiteen vurderer også om der skal ske tilbagemelding til slægtninge til en afdød forsøgsperson eller til en forsøgsperson, som har frabedt sig tilbagemelding om helbredsmæssige fund, hvis en variant opfylder de fem kriterier

Komiteen vurderer om der er behov for validering af varianten, hvilket typisk vil være tilfældet for varianter påvist ifm forsøg.

For varianter hvor komiteen vurderer at der skal ske en tilbagemelding til en forsøgsperson, beslutter komiteen på hvilken måde tilbagemeldingen skal ske, fx via den projektansvarlige eller via en klinisk genetisk afdeling.

Der udarbejdes en skriftlig rapport med konklusion om hver enkelt variant, som komiteen har foretaget en vurdering af.

Medlemmer og organisering
Komiteen nedsættes af klinikledelsen i Klinisk Genetisk Klinik, Rigshospitalet og består af mindst tre medlemmer med ekspertise indenfor medicinsk genetik og genetisk rådgivning og omfatter læger (klinisk genetikere og pædiatere) og molekylærbiologer (klinisk laboratoriegenetikere).

Litteratur
"Vejledning om genomforskning", NVK 2018

Kontakt

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How to proceed

- Contact the Department of Clinical Genetics
  - Contract
  - Data transfer agreement

} Legal department, Capital Region of Denmark