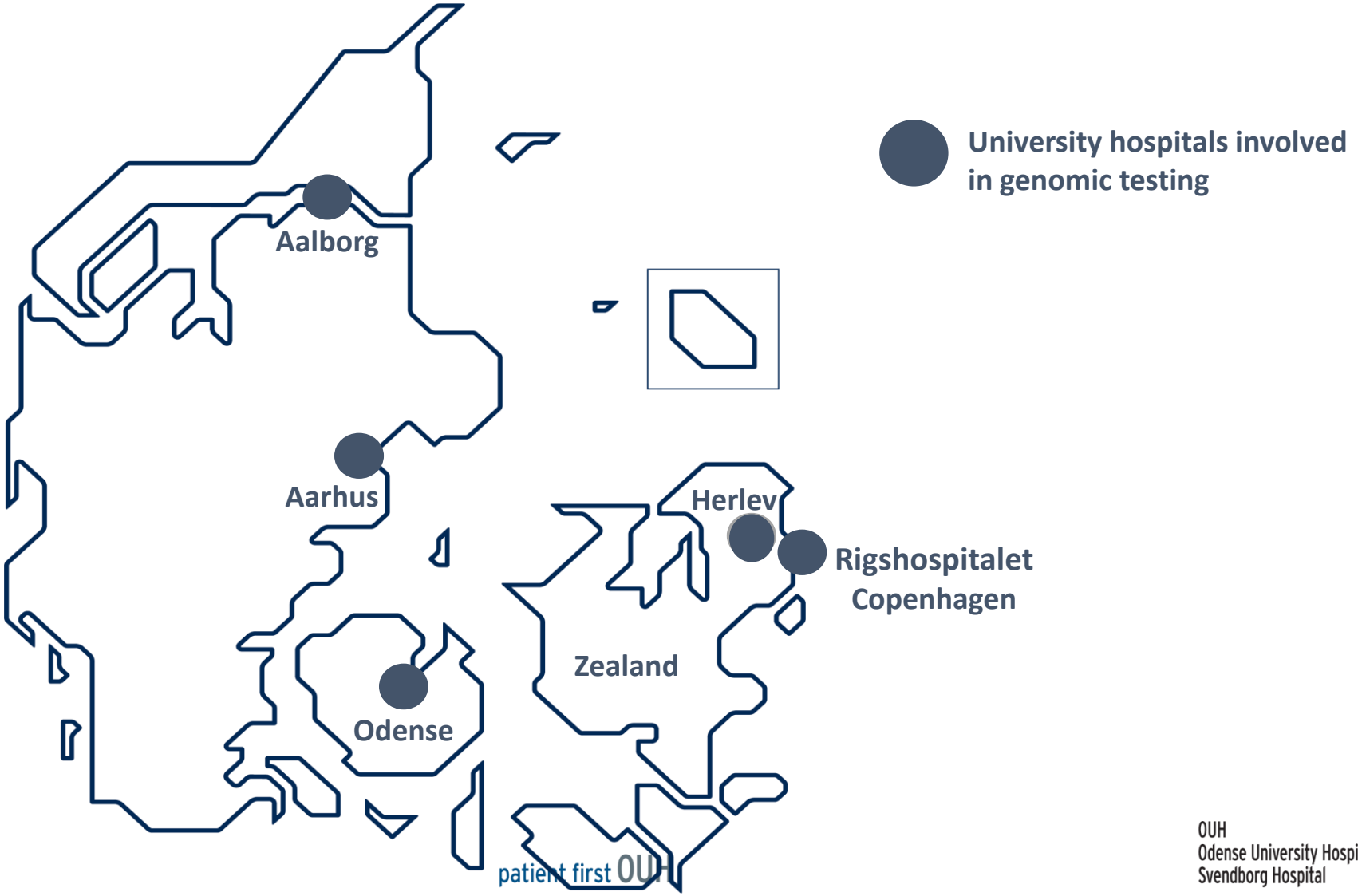
Precode: a precision medicine program in oncology in Region of Southern Denmark and its coordination with similar efforts at other Danish cancer units and the Danish National Genome Center.

Henrik J. Ditzel

Professor, Chief physician, Head of Research

Dept. of Oncology, Odense University Hospital and University of Southern Denmark

Precision medicine in Oncology in Denmark

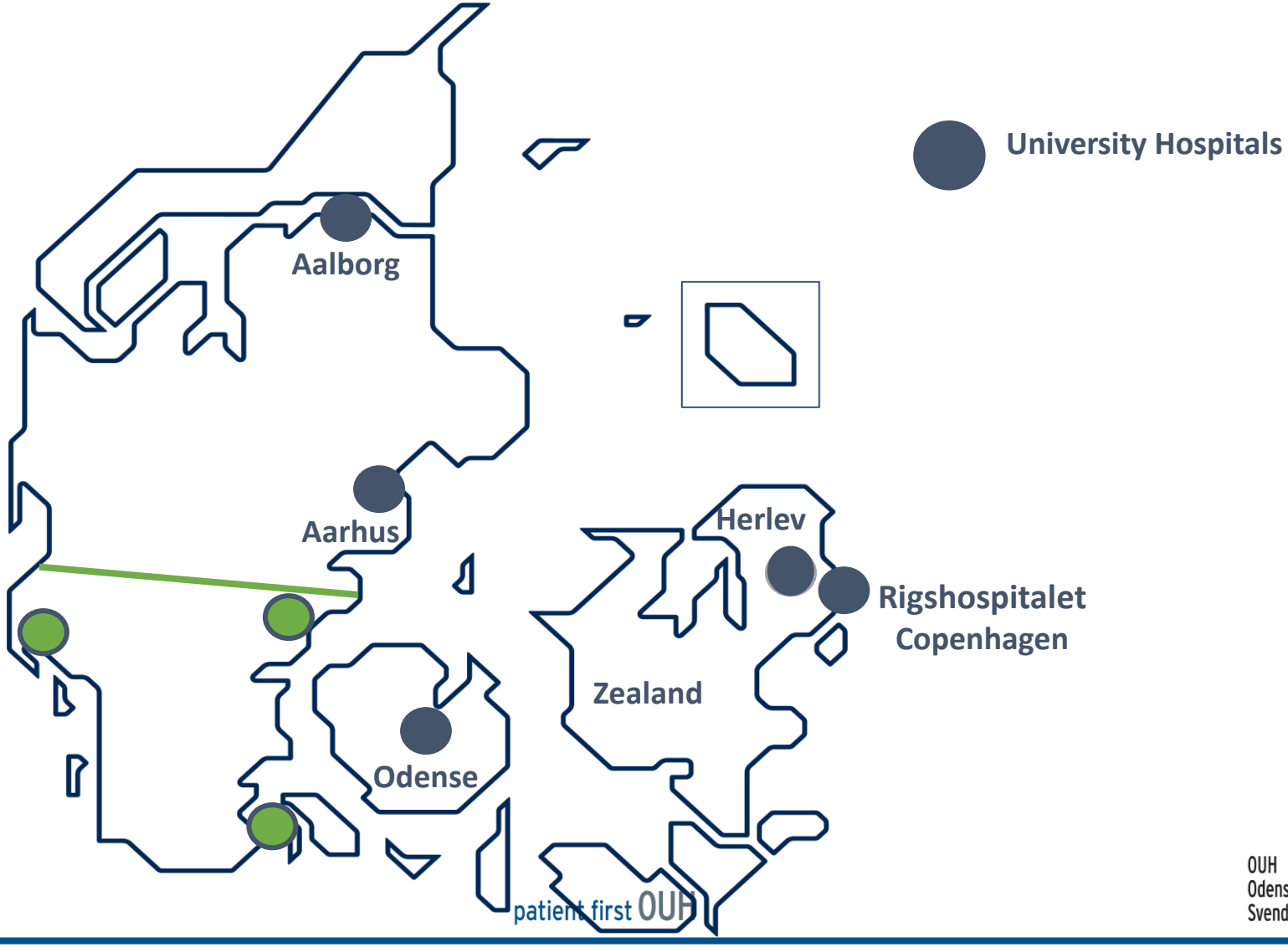


Region of Southern Denmark

patient first OUH

OUH
Odense University Hospital
Svendborg Hospital

Precision medicine in Oncology in Region of Southern Denmark



Region of Southern Denmark

patient first OUH

OUH
Odense University Hospital
Svendborg Hospital

PREcision medicine in Cancer in Odense, Denmark

PRECODE

The strategy of personalized medicine in oncology requires genomic profiling of the primary tumor or metastatic lesions

- Treatment is tailored to the molecular profile of the tumor
- But do we have matching targeted drugs available when genomic mutations are identified?
- Patients are not guaranteed an experimental treatment after genomic examination
- Shared decision making important

PREcision medicine in Cancer in Odense, Denmark

PRECODE

Background:

- In Dec 2016, the Danish Regions published a national strategy for Personal Medicine
  - This is a high priority area
- Few cancer patients from OUH were referred to the Phase 1 unit and the health authority's second opinion committee when the treatment options are exhausted
  - long case management is unsatisfactory for patients (6-8 weekes)
- The Region of Southern Denmark has granted money for genomic examination of 700 cancer patients annually
- During 2018 Dept. of Clinical Pathology, OUH, has established a setup around gene panel analysis
- Dept. of Oncology has expanded the experimental unit
- Local and National cooperation has been established

PRECODE a prospective cohort study

PRECODE

Purpose:

- to **evaluate a new infrastructure** for the investigation of patients with incurable cancer where treatment options are depleted

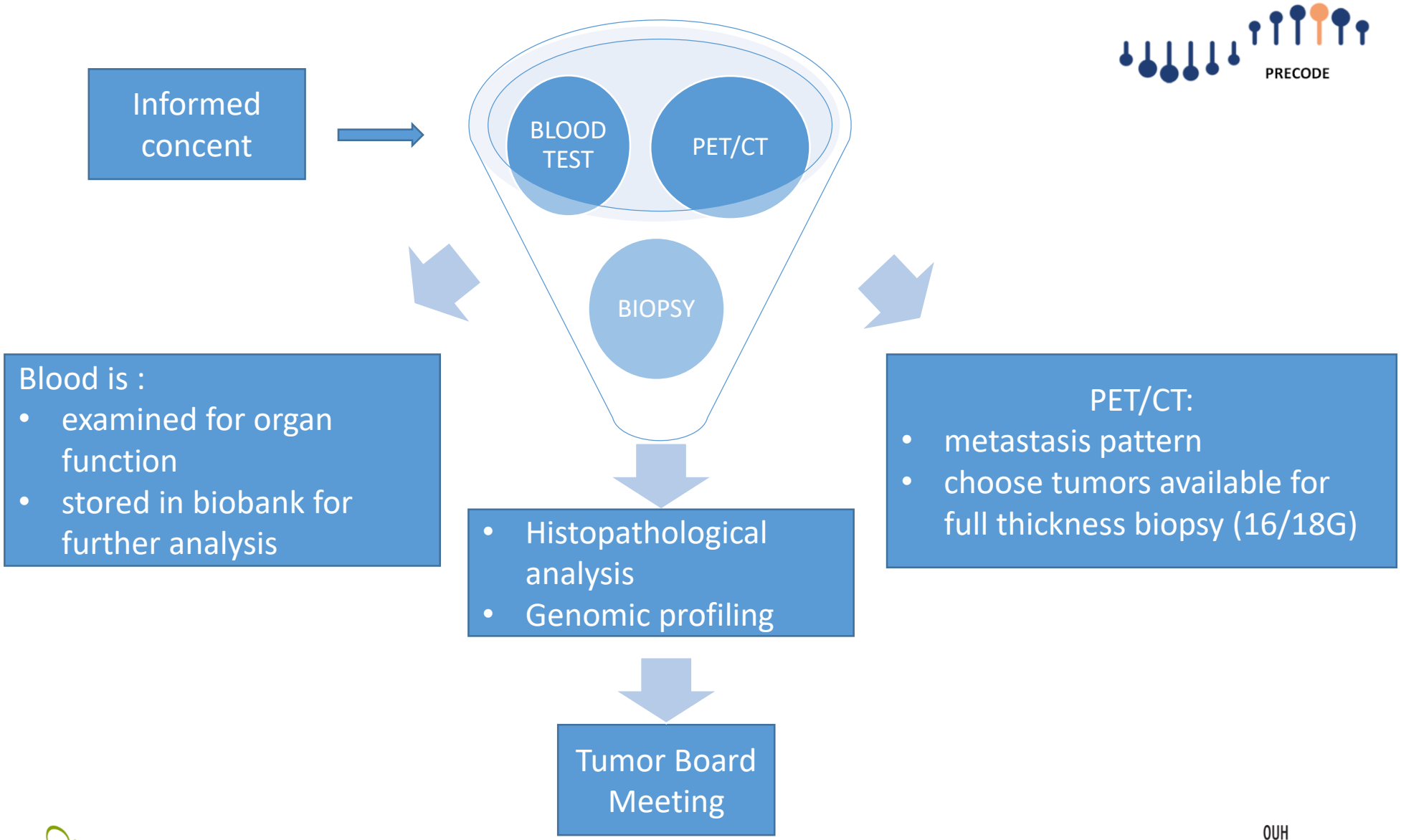
- to investigate whether **genetic changes** in the patients' tumor tissue can **give rise to an experimental treatment** offer

Inclusion Criteria in PRECODE

PRECODE

- Age > 18 år
- The participant provides written informed consent
- Solid tumor (all types) of patients who are not eligible for curative treatment
- No standard treatment available
- Performance Status, PS, 0-2
- Adequate organ function
- Life expectancy of at least 3 months

the patient is suitable for further treatment



Region of Southern Denmark

patient first OUH

OUH
Odense University Hospital
Svendborg Hospital

Oncomine Comprehensive Assay v3

Hotspot genes				Full-length genes			Copy number genes		Gene fusions (inter- and intragenic)		
AKT1	FOXL2	MET	AKT2	ATM	TP53	MSH6	AKT1	PPARG	ALK	RET	NF1
ALK	GATA2	MTOR	AKT3	BAP1	TSC1	NBN	AR	TERT	AXL	ROS1	NOTCH1
AR	GNA11	MYD88	AXL	BRCA1	TSC2	NOTCH2	CCND1	AKT2	BRAF	AKT2	NOTCH4
ARAF	GNAQ	NFE2L2	CCND1	BRCA2	ARID1A	NOTCH3	CCNE1	AKT3	EGFR	AR	NRG1
BRAF	GNAS	NRAS	CDK6	CDKN2A	ATR	PALB2	CDK4	ALK	ERBB2	BRCA1	NTRK2
BTK	HNF1A	PDGFRA	ERCC2	FBXW7	ATRX	PMS2	CDK6	AXL	ERG	BRCA2	NUTM1
CBL	HRAS	PIK3CA	FGFR4	MSH2	CDK12	POLE	EGFR	BRAF	ETV1	CDKN2A	PDGFRB
CDK4	IDH1	PPP2R1A	H3F3A	NF1	CDKN1B	RAD50	ERBB2	CCND2	ETV4	ERBB4	PIK3CA
CHEK2	IDH2	PTPN11	HIST1H3B	NF2	CDKN2B	RAD51	FGFR1	CCND3	ETV5	ESR1	PRKACA
CSF1R	JAK1	RAC1	MAP2K4	NOTCH1	CHEK1	RAD51B	FGFR2	CDK2	FGFR1	FGR	PRKACB
CTNNB1	JAK2	RAF1	MDM4	PIK3R1	CREBBP	RAD51C	FGFR3	CDKN2A	FGFR2	FLT3	PTEN
DDR2	JAK3	RET	MYC	PTCH1	FANCA	RAD51D	FGFR4	CDKN2B	FGFR3	JAK2	RAD51B
EGFR	KDR	RHEB	MYCN	PTEN	FANCD2	RNF43	FLT3	ESR1	NTRK1	KRAS	RB1
ERBB2	KIT	RHOA	NTRK1	RB1	FANCI	SETD2	IGF1R	FGF19	NTRK3	MDM4	RELA
ERB83	KNSTRN	SF3B1	NTRK2	SMARCB1	MLH1	SLX4	KIT	FGF3	PDGFRA	MET	RSPO2
ERBB4	KRAS	SMO	PDGFRB	STK11	MRE11A	SMARCA4	KRAS	NTRK1	PPARG	MYB	RSPO3
ESR1	MAGOH	SPOP	PIK3CB				MDM2	NTRK2	RAF1	MYBL1	TERT
EZH2	MAP2K1	SRC	ROS1				MDM4	NTRK3			
FGFR1	MAP2K2	STAT3	SMAD4				MET	PDGFRB			
FGFR2	MAPK1	U2AF1	TERT				MYC	PIK3CB			
FGFR3	MAX	XPO1	TOP1				MYCL	RICTOR			
FLT3	MED12						MYCN	TSC1			
							PDGFRA	TSC2			
							PIK3CA				

Figure 1. List of gene targets in Oncomine Comprehensive Assay v3. Genes in blue are additional targets in the Oncomine Comprehensive Assay v3 that were not included in the first version.

Covers 161 of the most relevant cancer driver genes

Result of genpanel analysis is discussed on tumor board meeting

PRECODE

Tumor Board OUH & National

Genomic mutations identified

- Fase I, II, III trials
- Off label treatment
- Best supportive care

No genomic mutations

- Clinical trials
- Less evidens-based treatment
- Best supportive care

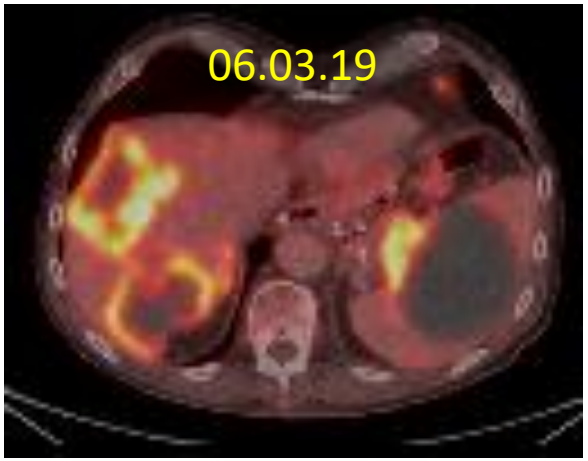
Experimental protocols have first priority

PRECODE status

- Study initiated 01.03.19
- First patient included 04.03.19
- Patient no 136 included 08.10.19

Patient no. 1 PRECODE

- Metastatic recurrence of gastric cancer
  - adenocarcinoma
- Liver and spleen matastases
- 2 lines of chemotherapy
- Treatment options are depleted
- 04.03.19: informed concent PRECODE
- PET/CT: 06.03.19
- Liver biopsy 11.03.19
- Tumor board 18.03.19



Result of gene panel analysis

PRECODE

OUH
Odense Universitetshospital
Svendborg Sygehus

Region Syddanmark

Molekylærpatologisvar

20.03.19: informed consent in a Fase 2, PARB inhibitor Olaparib study

The gene panel analysis resulted in a possible treatment offer.....

NOTCH2	c.4999G>A	p.Val1667Ile	12% (1770/230)
PIK3CB	c.3200A>T	p.Asp1067Val	14% (1714/283)
BRCA2	c.8878C>T	p.Gln2960Ter	12% (1765/235)

Starting point: Many patients suffer from inadequate health care treatment as drugs are ineffective

(FDA ”Paving the way for personalized medicine”, 2013)

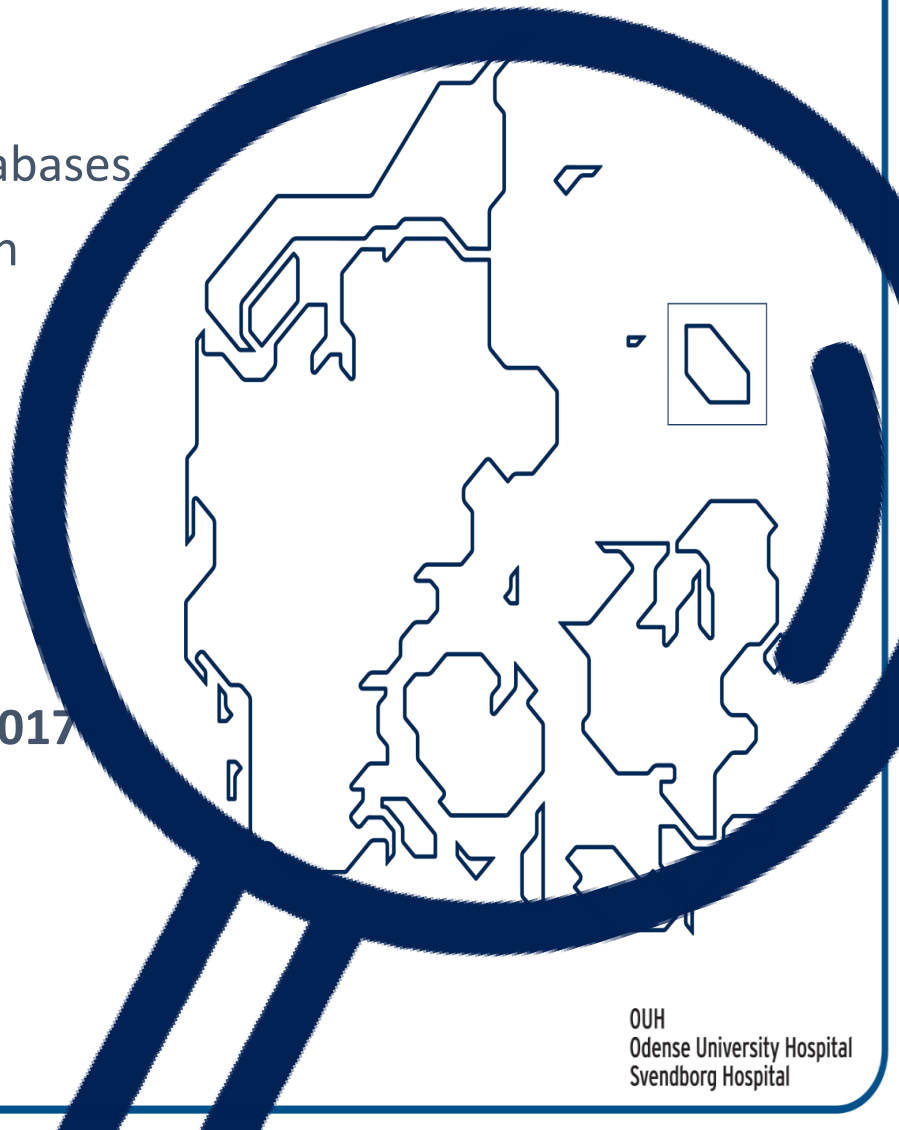
The Danish Landscape for Precision Medicine

Danish strongholds

- National registries, biobanks and quality databases
- IT- infrastructure and high level of digitisation
- Strong research traditions
- A large life science industry
- Many relevant activities within and across healthcare and research

National Strategy for Personalised Medicine 2017-2020

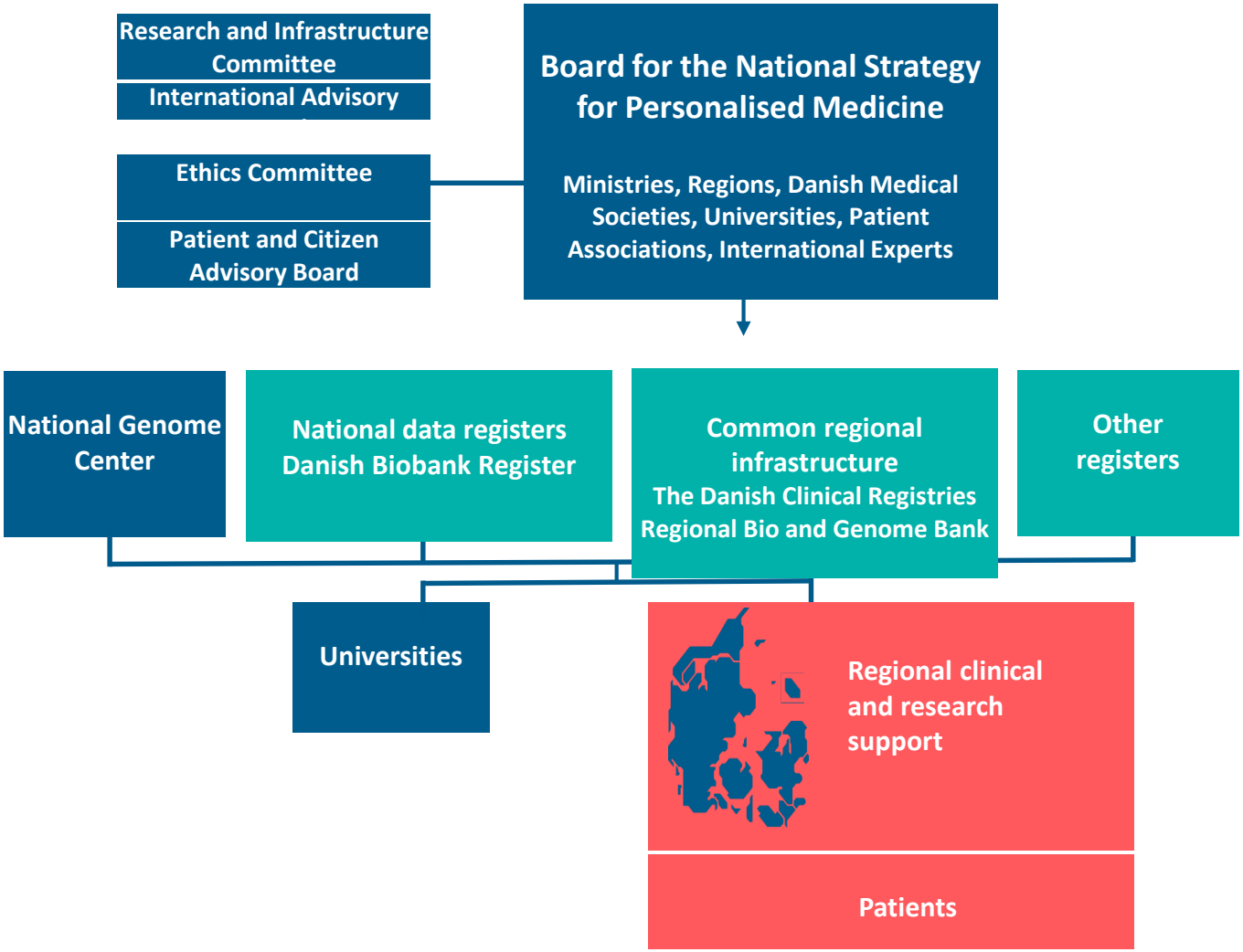
- National governance structure
- Danish National Genome Centre (NGC)



The vision for Danish National Genome Center

- Better use of new technologies and knowledge about genetics
- Support to doctors and researchers to achieve knowledge about genes so we can understand disease better and it becomes possible to diagnose more precisely and target treatment more accurately
- Through research carried out with the many we can make a difference for the individual

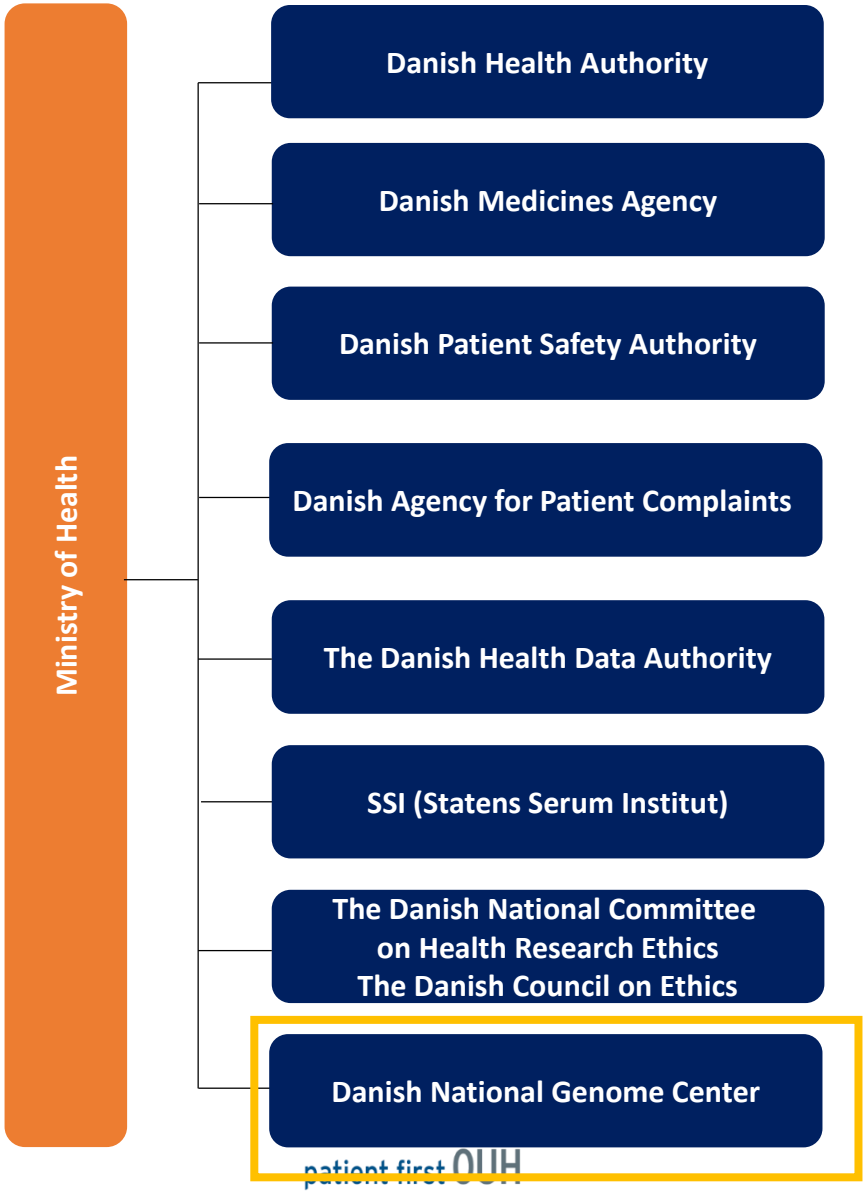
Governance for The National Strategy for Personalised Medicine



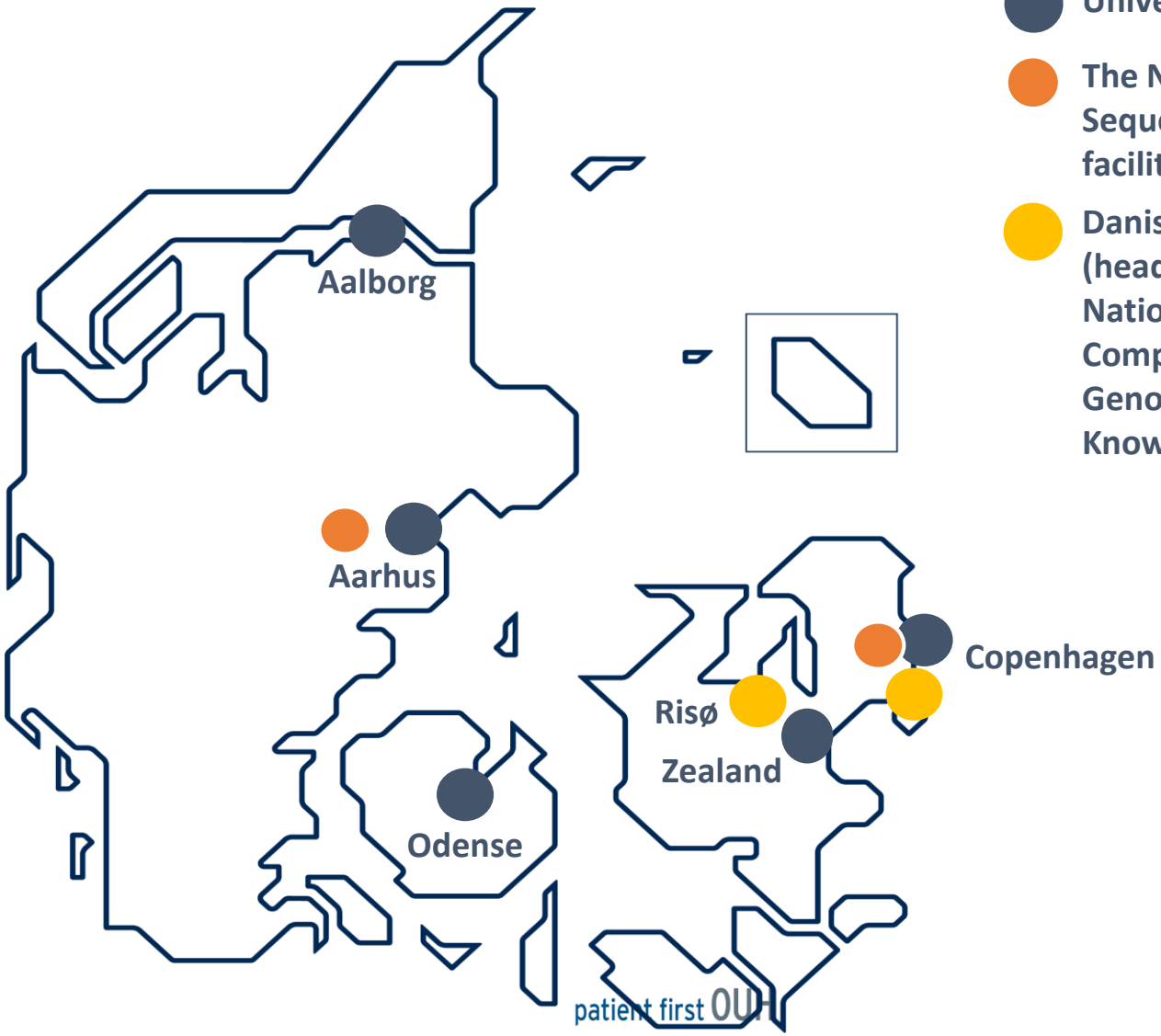
New government agency and an authority

- Danish National Genome Center (NGC) is a new government agency and an authority within the Danish Healthcare system.

- NGC's primary task is to lay the foundation for the development of better diagnostics and more targeted treatments for patients using whole-genome sequencing (WGS).



Danish National Genome Center: Infrastructure for precision medicine



- University Hospitals
- The National Whole Genome Sequencing (WGS) Center facilities east and west
- Danish National Genome Center (headquarter) and National High Performance Computing (incl. National Genome Database and National Knowledge Databases)

Region of Southern Denmark

patient first OUH

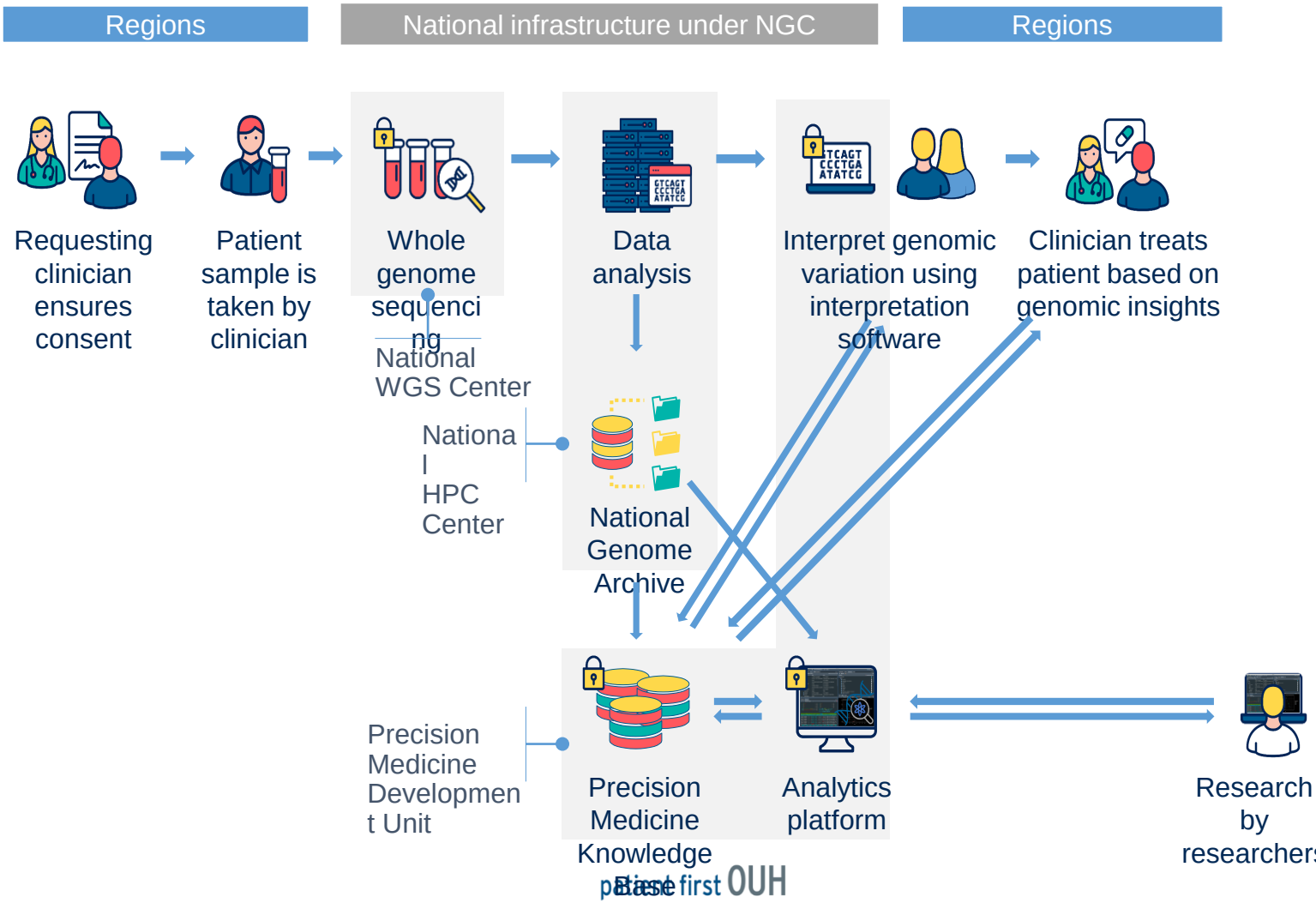
OUH
Odense University Hospital
Svendborg Hospital

Regional data support centers

- Counseling and sparring on clinical use as well as suggestions for research, development and implementation projects.
- Sample collection and biobanking
- Data generation - genomic and clinical data
- Data retention - genomic and clinical data
- Data analysis - biostatistics and bioinformatics
- Data interpretation

Relationship between elements in the infrastructure

Illustrates points of entry to NGC where data is either uploaded or accessed with strict security mechanisms implemented

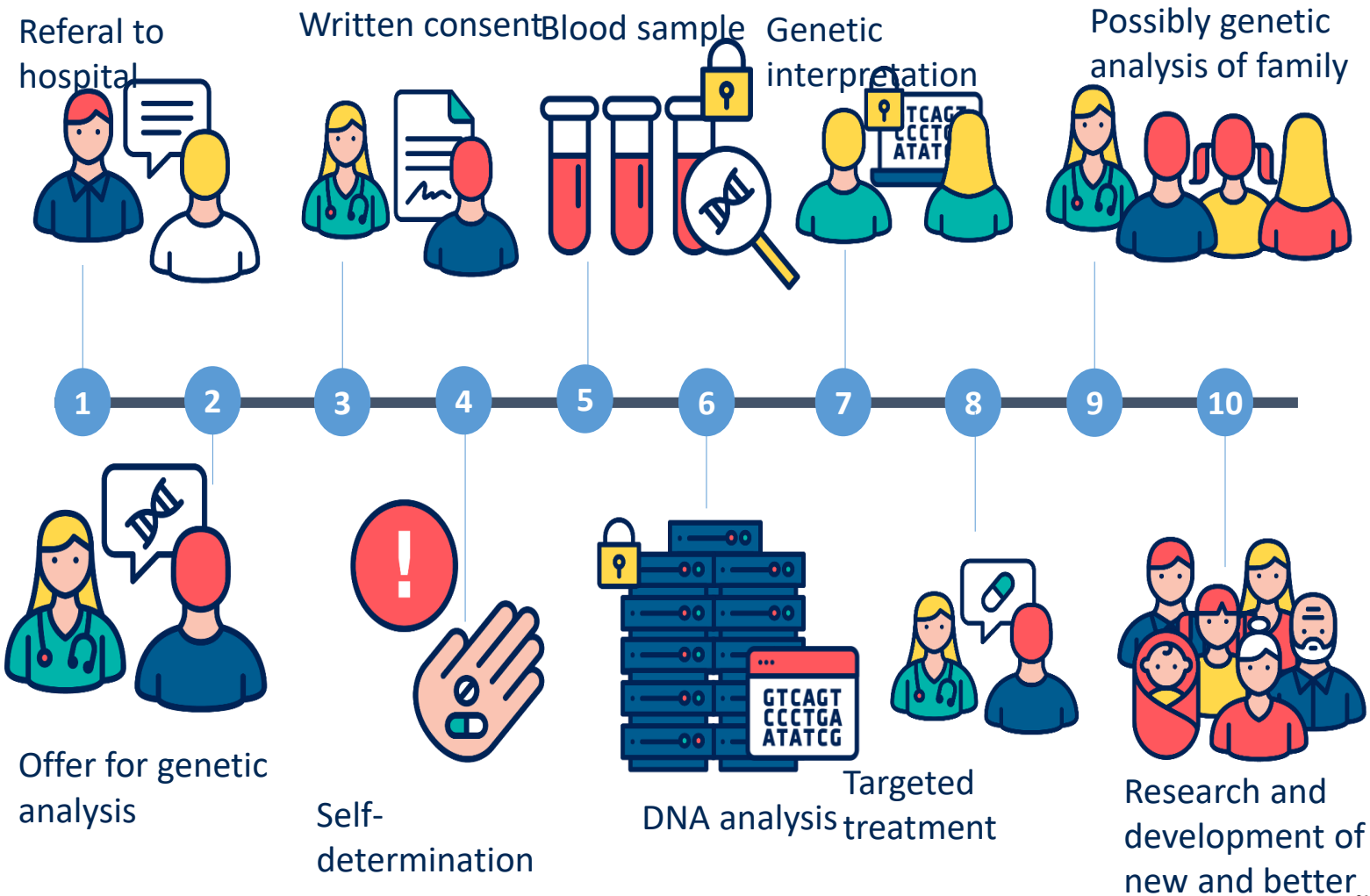


Region of Southern Denmark

Patient first OUH

OUH Odense University Hospital Svendborg Hospital

The course of a patient gene test – step by step



Thank you for your attantion!