Pediatric Cardiac Surgery: Past, Present, and Future

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CHOI

“Any surgeon who wishes to preserve the respect of his colleagues would never attempt to operate on the heart.”

(Theodore Billroth)

Evolution of Congenital Cardiac Surgery

4 eras complete, 1 in process, more to come

Closed extra-cardiac operations	1937
Early closed or semi-closed intra-cardiac operations	1944
Complete intra-cardiac repair	1952
Refinement of technique	1971
Management of unforeseen co-morbidities	2000
Disease causality risk assessment and surgical planning	2015
?	?

Evolution of Cardiac Surgery

4 historical eras

1. Closed extra-cardiac operations
    1937/8 - Ligation of patent ductus arteriosus (Strider and Gross)

2. Early closed or semi-closed intra-cardiac operations
    1944 - Coarctation repair (Craaford)
    1944 - Blalock-Taussig shunt
    1946 - Potts' shunt
    1946 - Closed pulmonary valvotomy (Sellors)
    1948 - Blalock-Hanlon atrial septectomy
    1952 - Pulmonary artery band (Muller and Dammann)

Evolution of Cardiac Surgery

4 historical eras

3. Complete intra-cardiac repair
    - 1952 - Atrial well for ASD closure (Gross)
    - 1952 - ASD closure with inflow occlusion and hypothermia (Lewis)
    - 1954 - Controlled cross-circulation (Lillehei)
    - 1958 - Superior cavopulmonary anastomosis (Glenn)
    - 1962 - Waterston's shunt
    - 1966 - Balloon atrial septostomy (Rashkind)
    - 1968 - Atriopulmonary connection (Fontan and Baudet)

Evolution of Cardiac Surgery

4 historical eras

4. Refinement of technique

1971 - Complex repair in neonates and infants with DHCA (Barratt-Boyes)

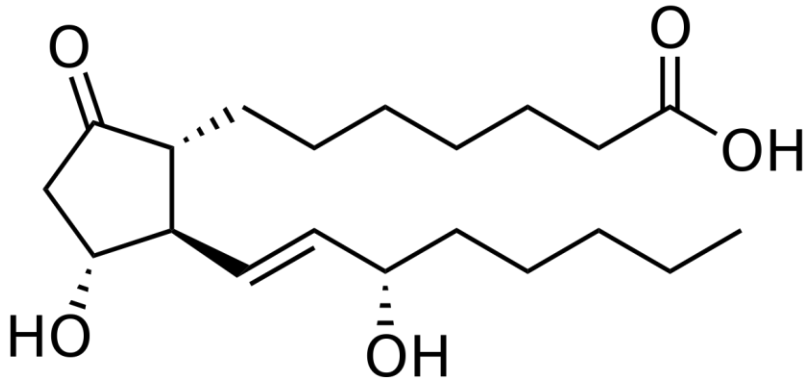
1975 - Arterial switch operation (Jatene)

1976 - Introduction of PGE_1 (Elliott)

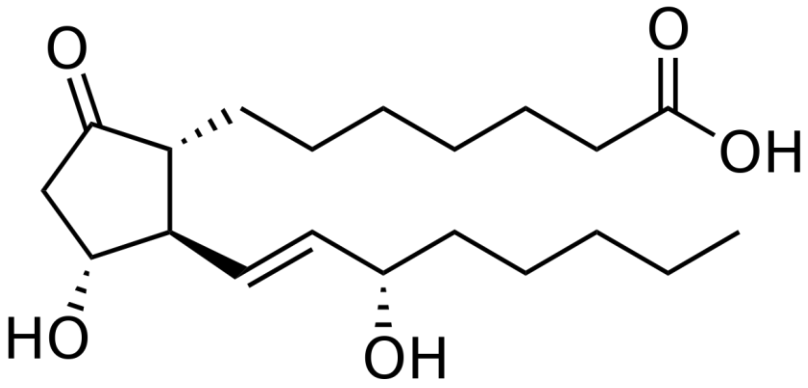
1981 –Stage I palliation of hypoplastic left heart syndrome (Norwood)

1984 - Neonatal heart transplantation (Bailey)

PGE_1



PGE_1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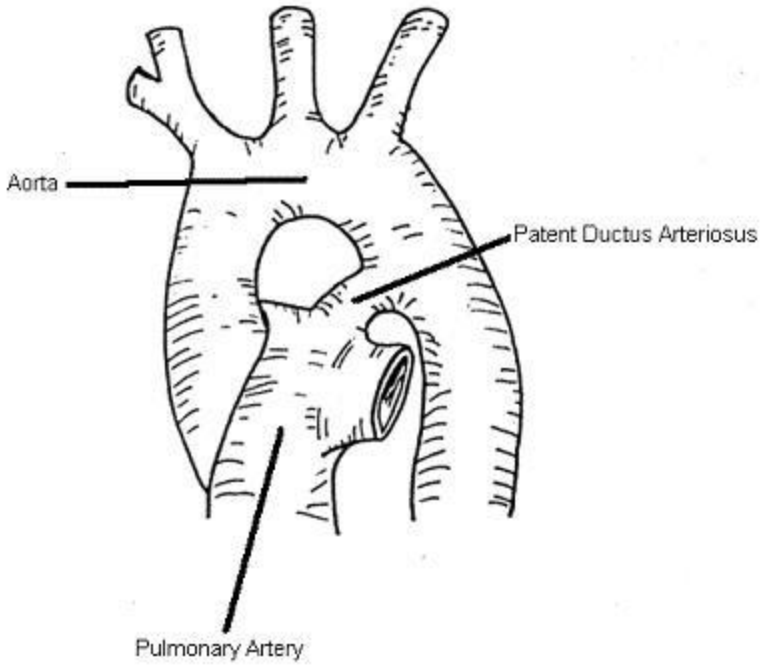
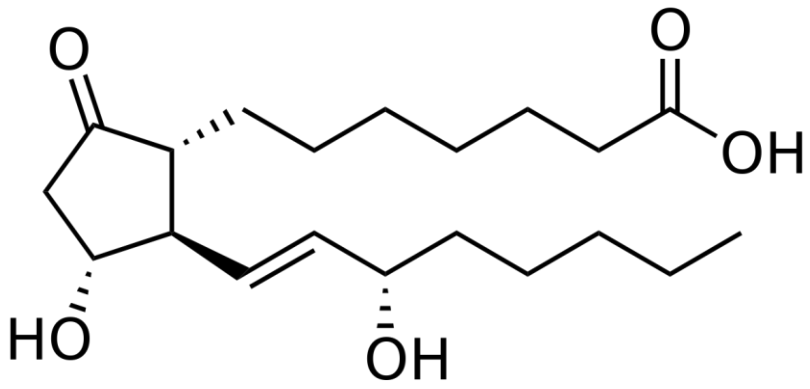

Aorta
Patent Ductus Arteriosus
Pulmonary Artery

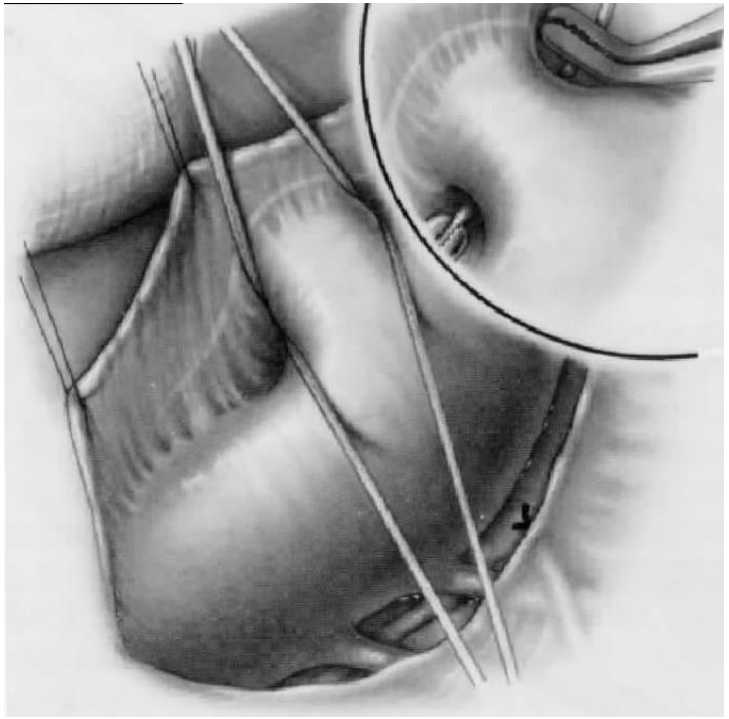
PGE_1



Surgeon

Ligation of patent ductus arteriosus

- 1937 John Stridor
- 1938 Robert Gross



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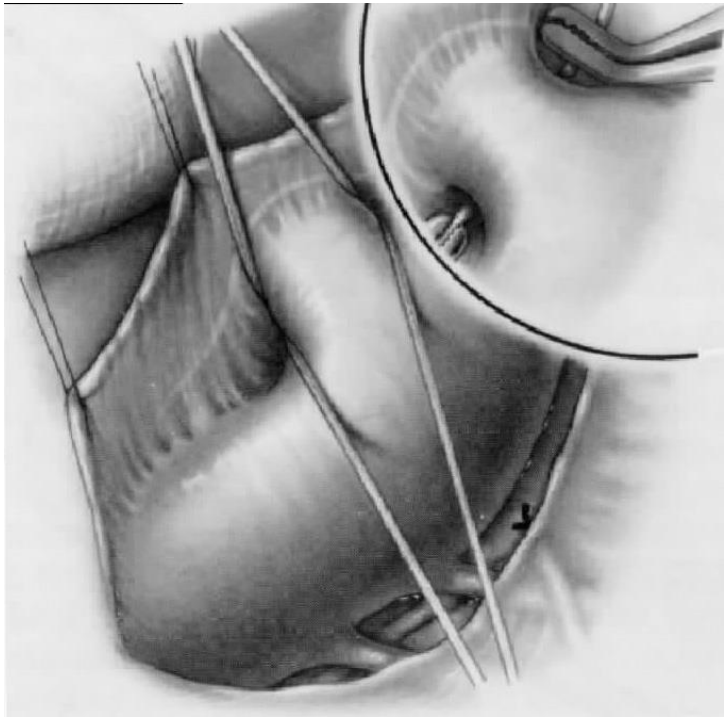
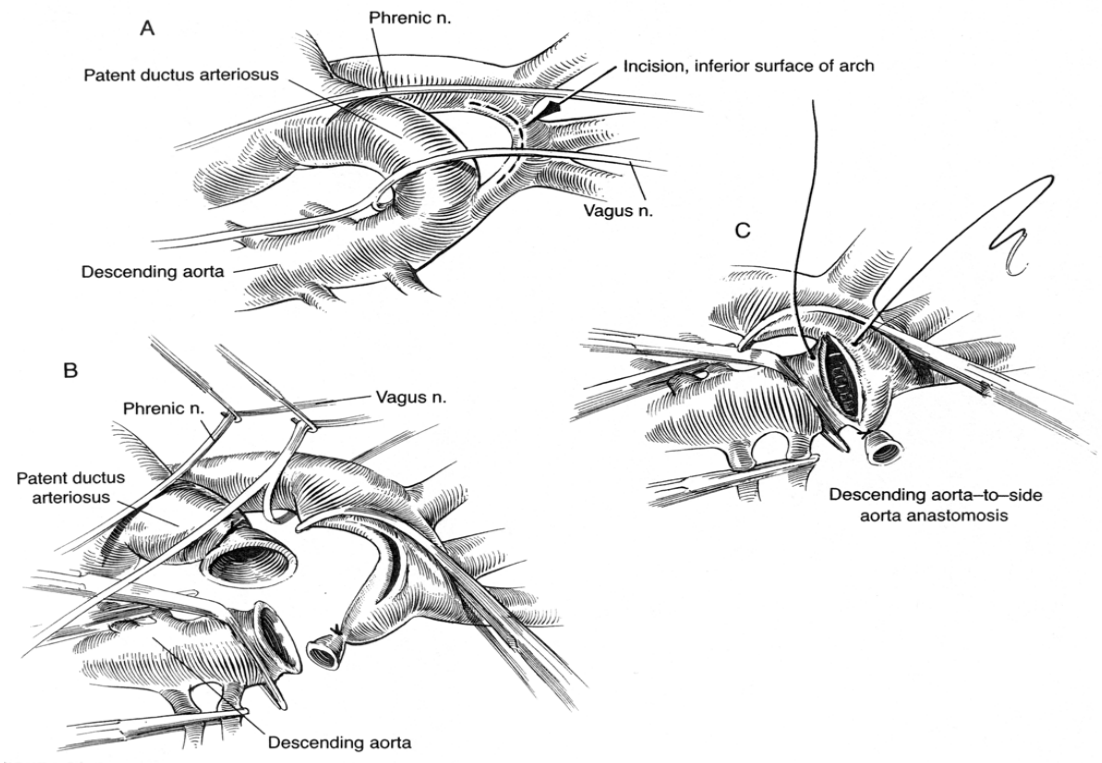
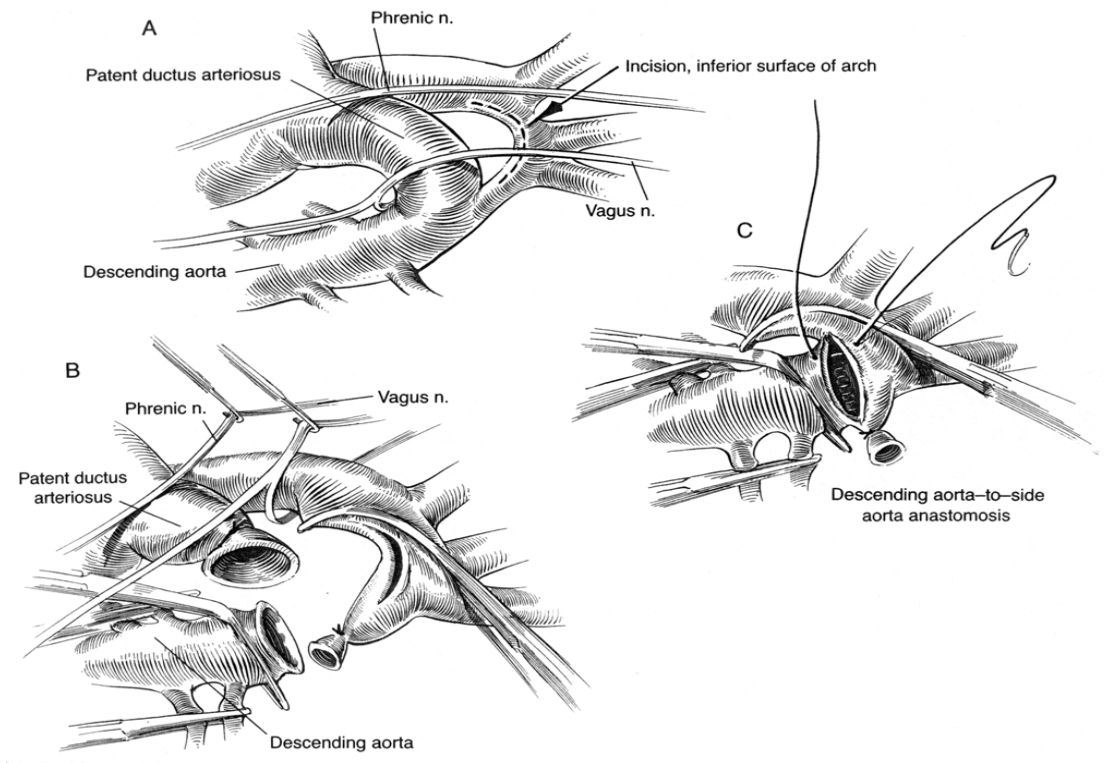


Coarctation of the aorta repair



- 1944 Blalock-Park
- 1944 Craaford

Coarctation of the aorta repair



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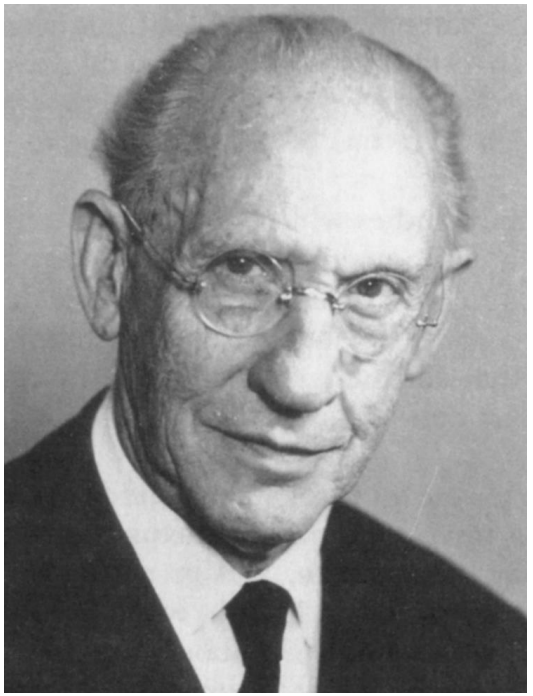
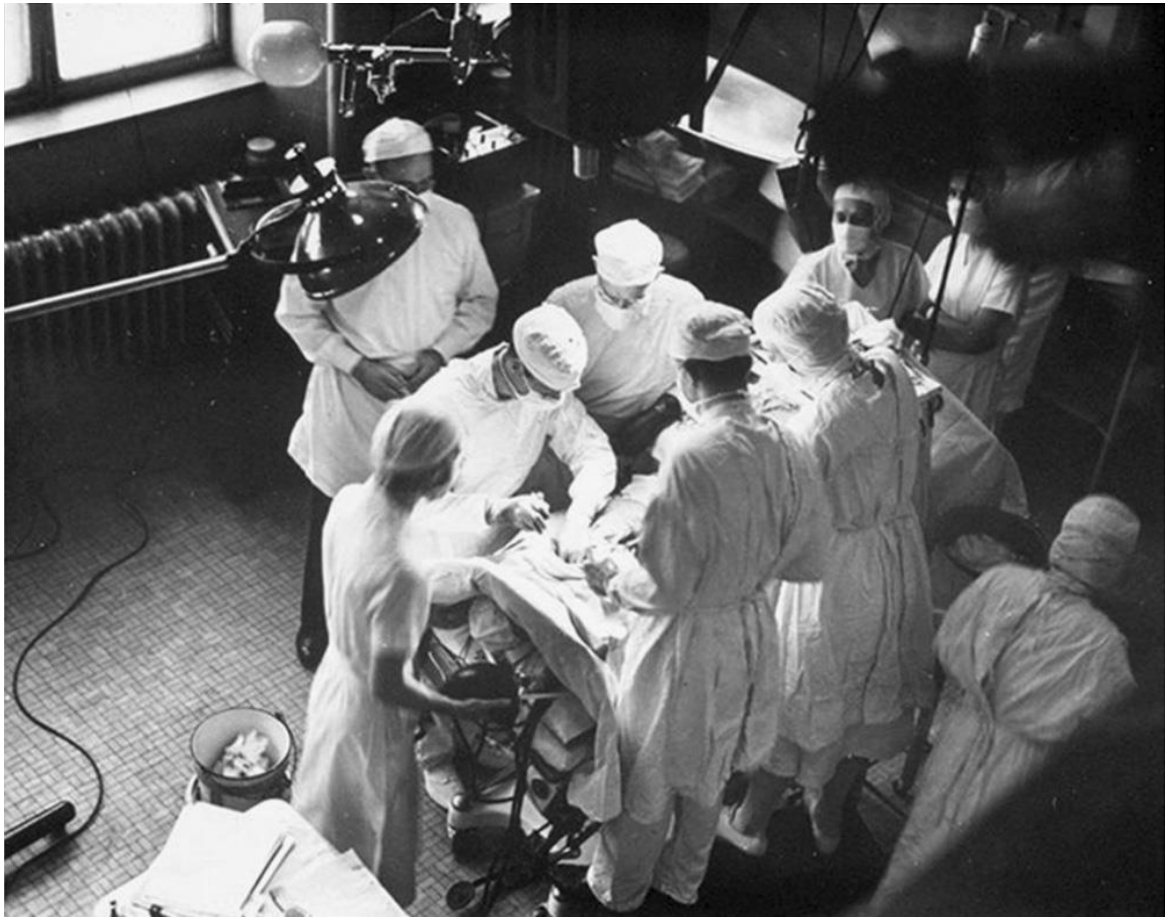
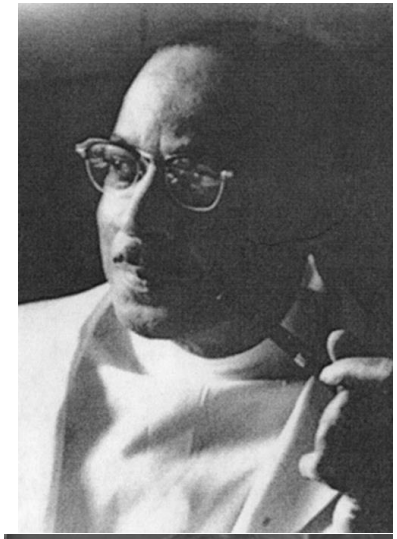


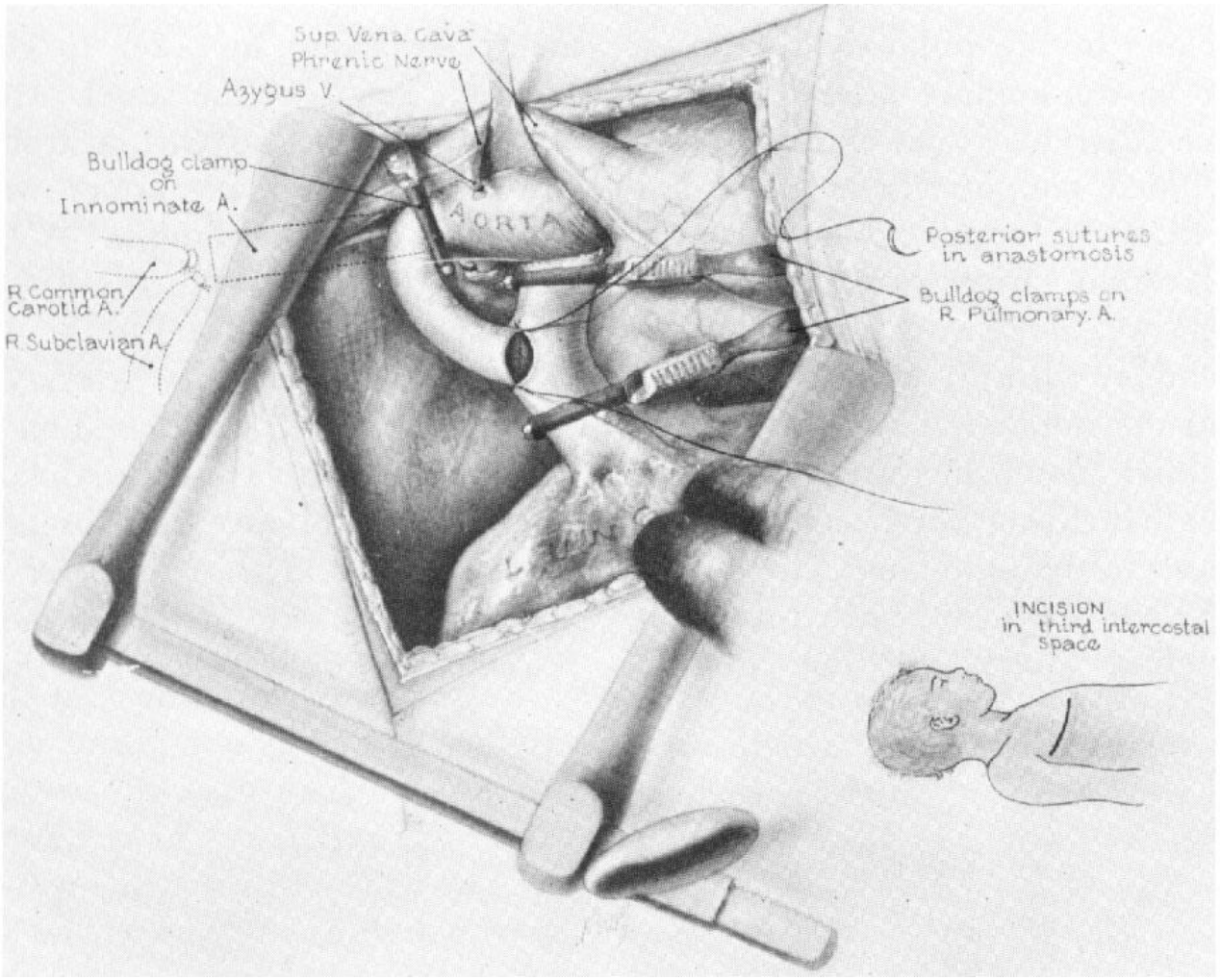
Johns Hopkins Hospital, 1945



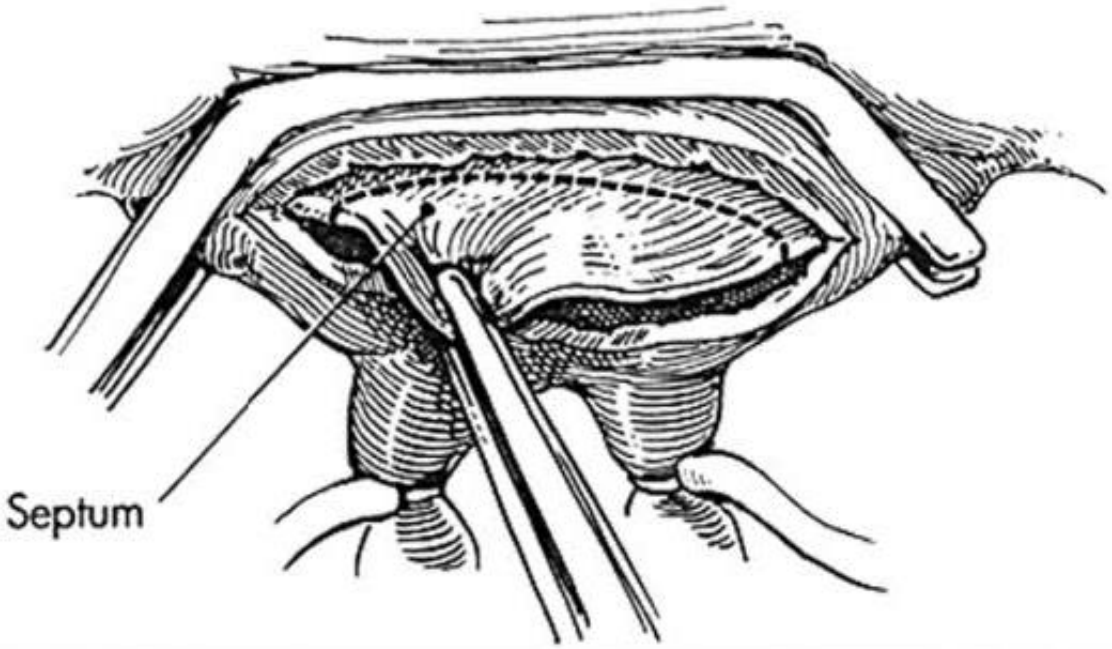
- Alfred Blalock
- Vivien Thomas
- William Longmire
- Denton Cooley

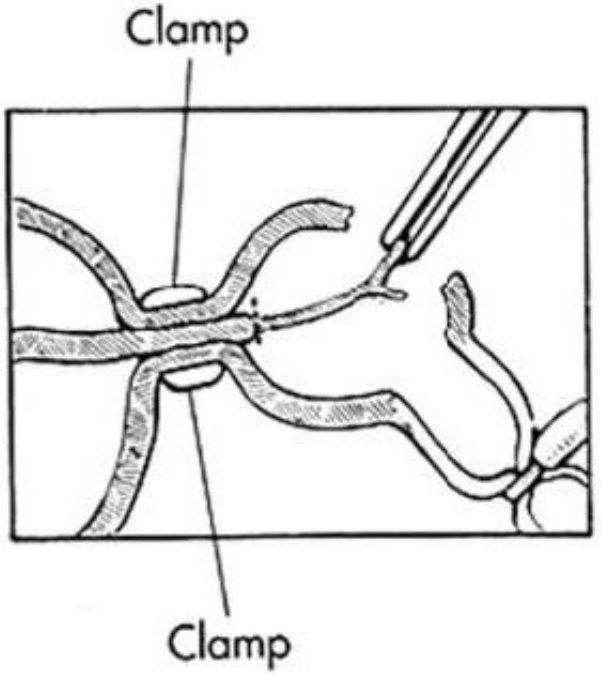
Palliation of cyanotic heart disease





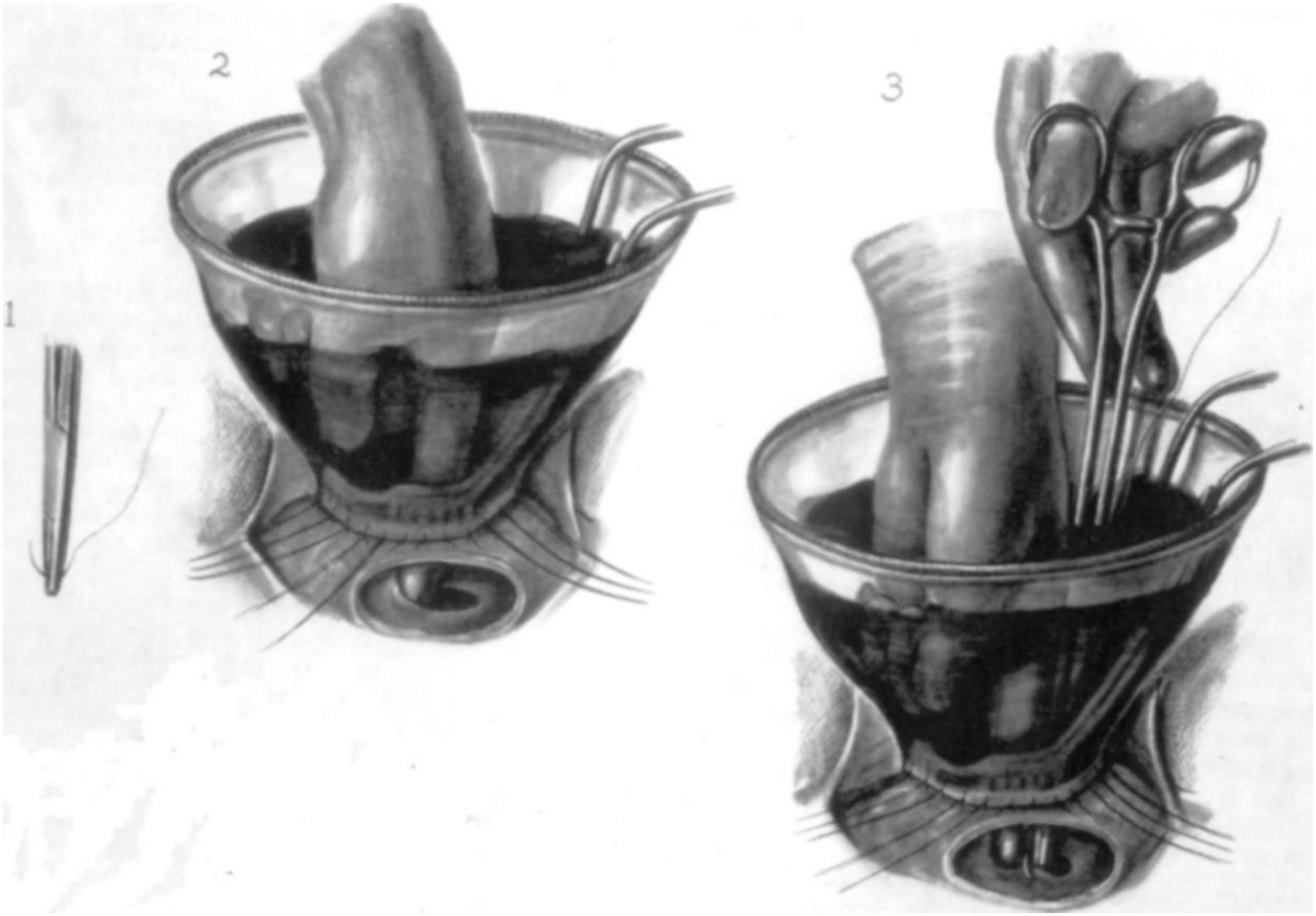
B-H atrial septectomy





Rashkind

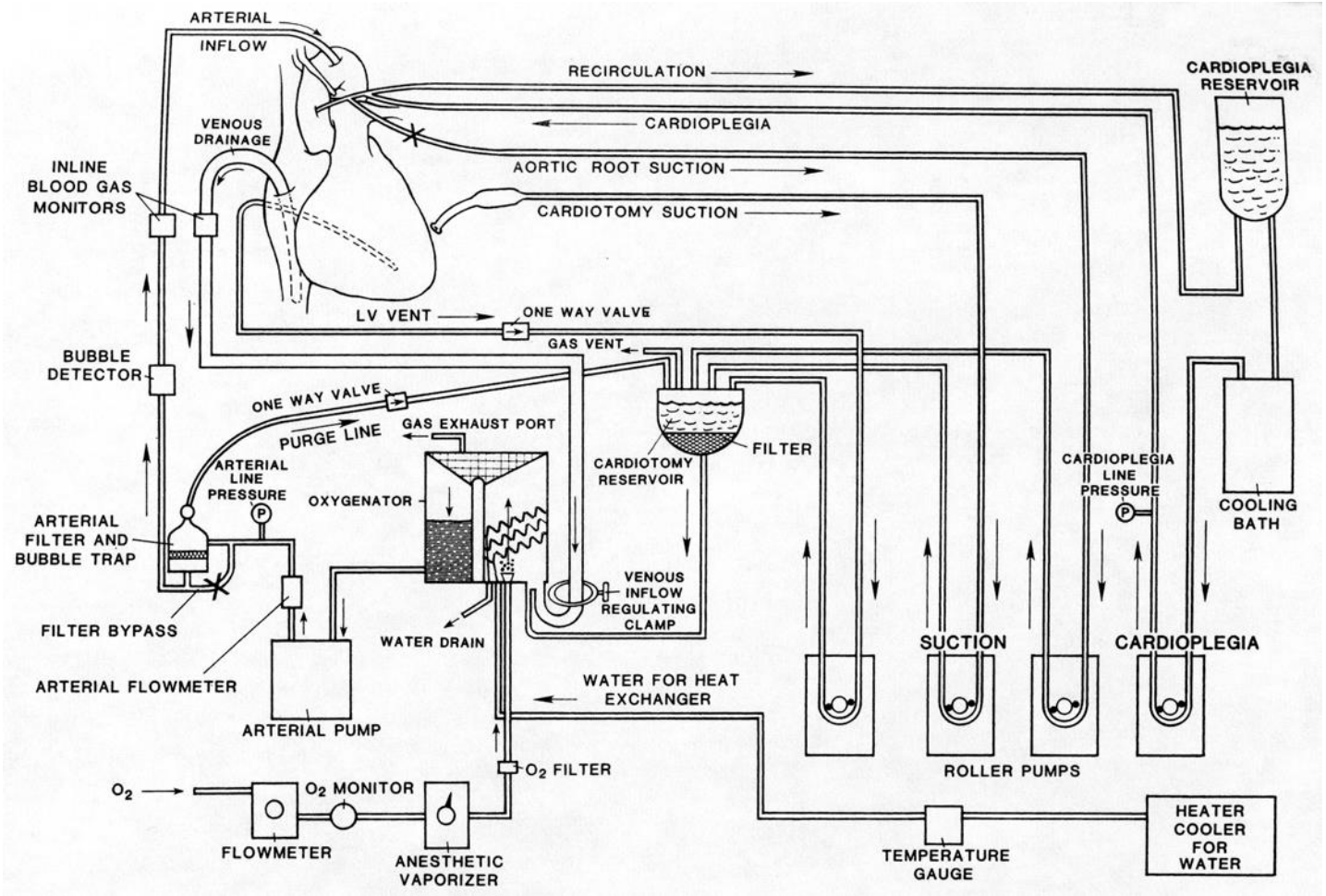
Atrial well technique of ASD closure- the wild west (Gross)



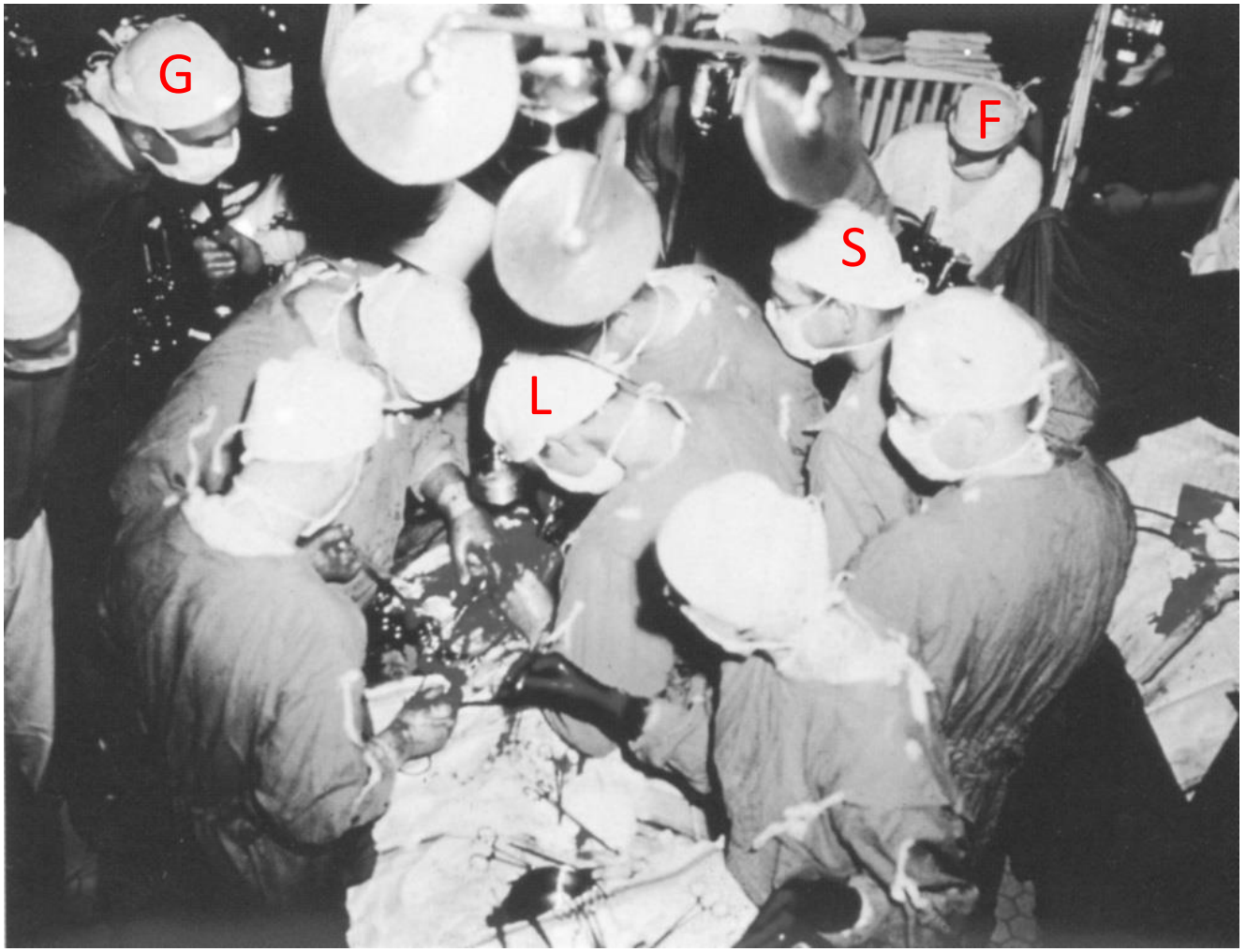
Evolution of ASD closure

Date	Surgeon	Technique	Institution	Mortality
1948	Murray	External suturing		
1952	Gross	Atrial well- blind!	Boston Children's	30.2%
1952	Lewis	Inflow occlusion	Mayo	12.1%
1953	Gibbon	Direct closure with CPB	Penn	
today	all	CPB	everywhere	<1%

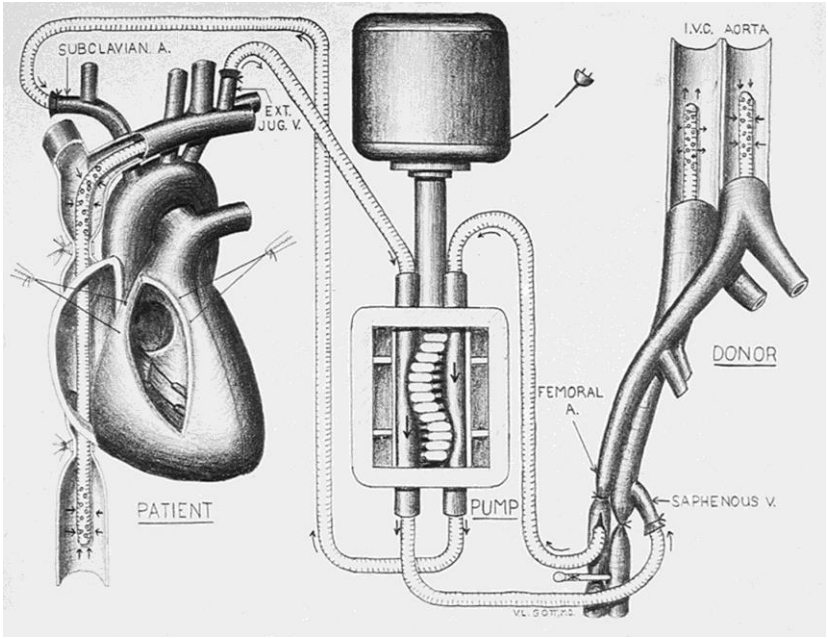
Cardiopulmonary Bypass Circuit



Cross circulation- Mayo experience

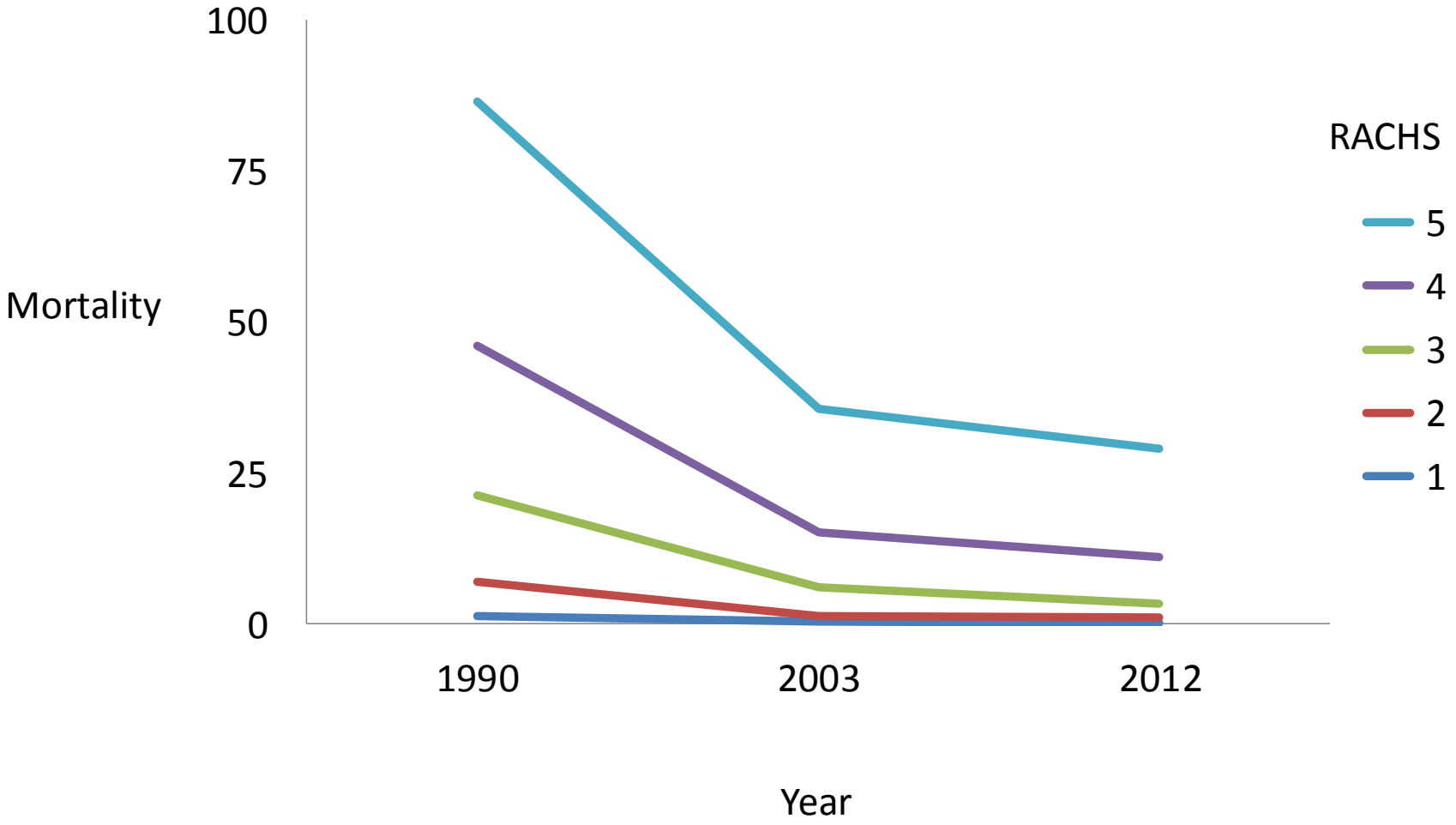


Cross circulation



- 1 y.o. 6.9 kg VSD, 11d survival
- support Owen Wangenstein
- 4 y.o. girl with a VSD
- 45 operations
- TOF, AVSD, VSD
- No operative deaths were directly attributable due to the cross circulation technique
- post-operative heart block was the real killer

Risk in Congenital Heart Surgery: Chronological improvement

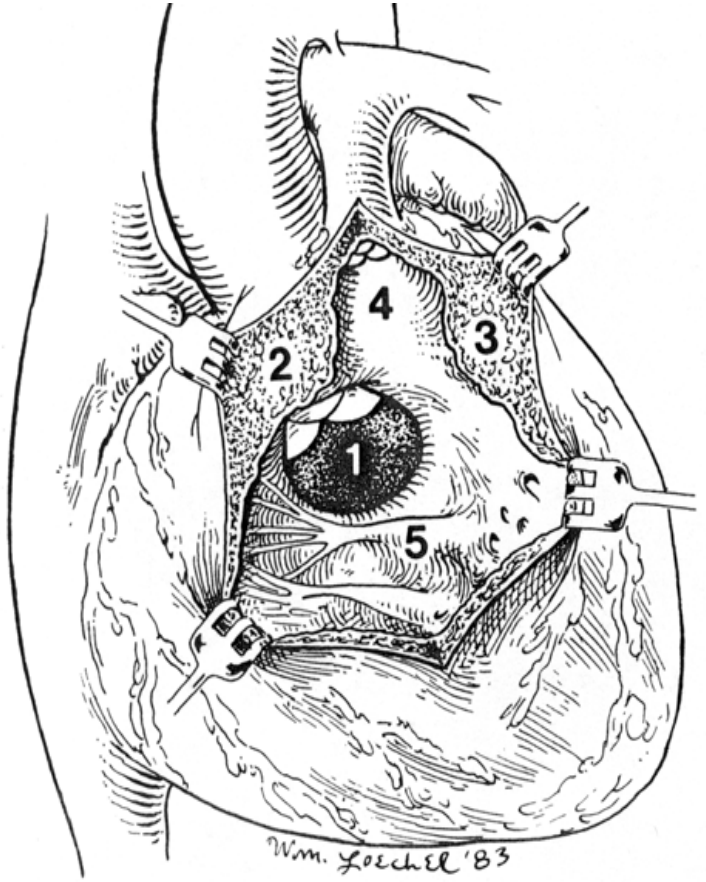


How do we crack the final percentage?

Today

- team oriented approach
- importance of co-morbidities
- operations for single ventricle physiology
- neurodevelopment
- fetal interventions

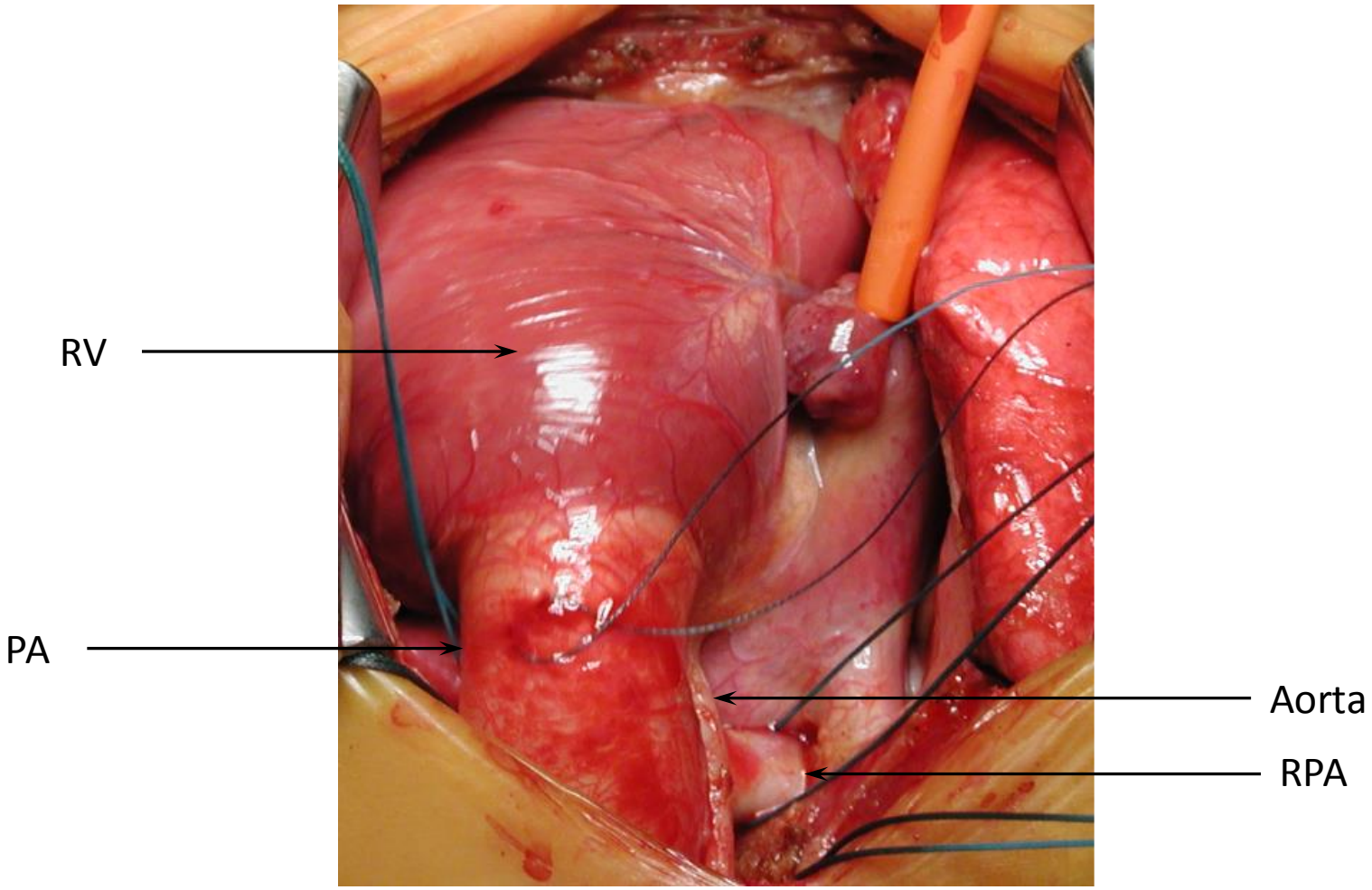
Tetralogy of Fallot



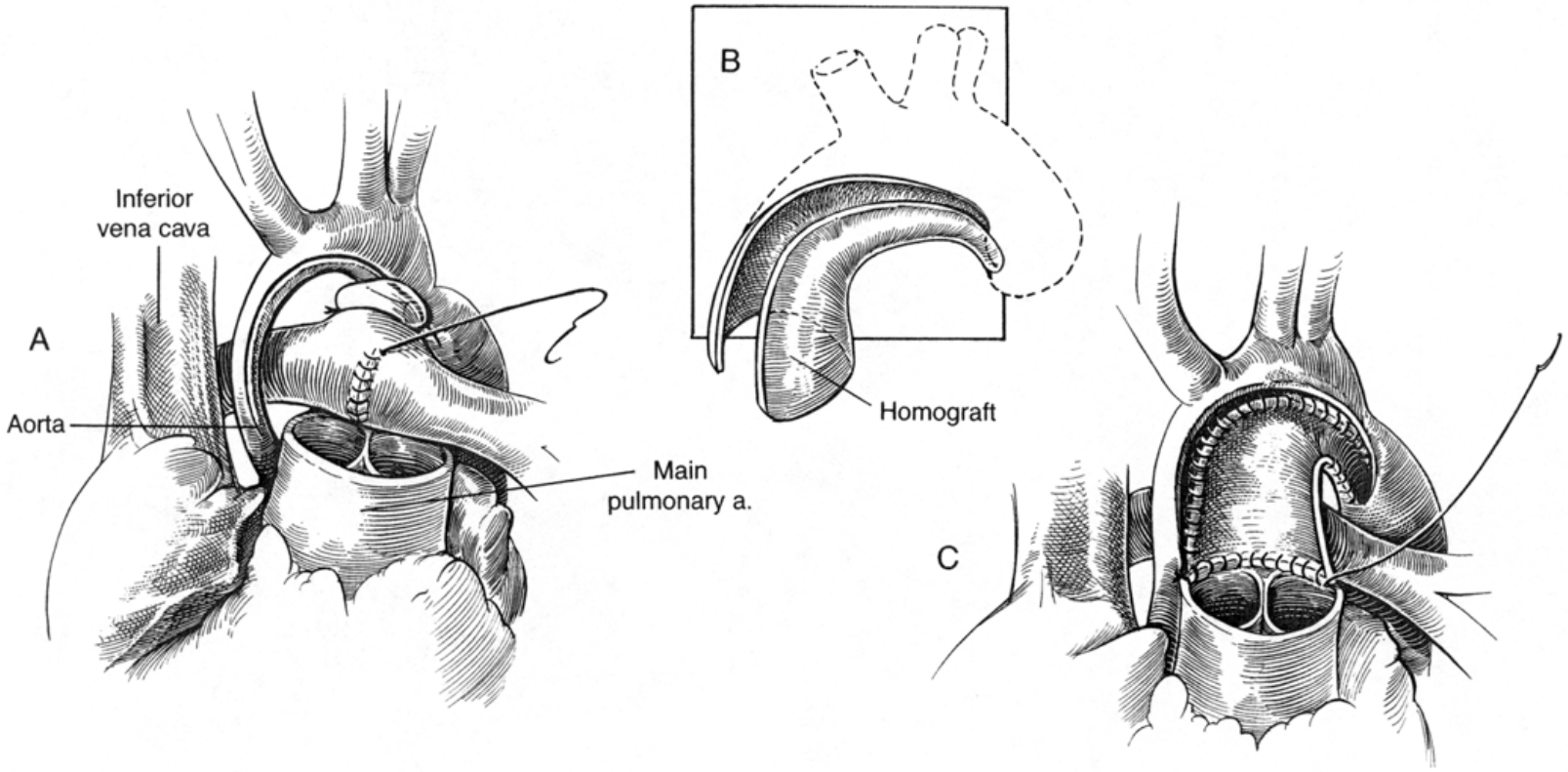
Patients with same disease have different responses

Post operative day 5, TOF

HLHS



HLHS- Classic Norwood



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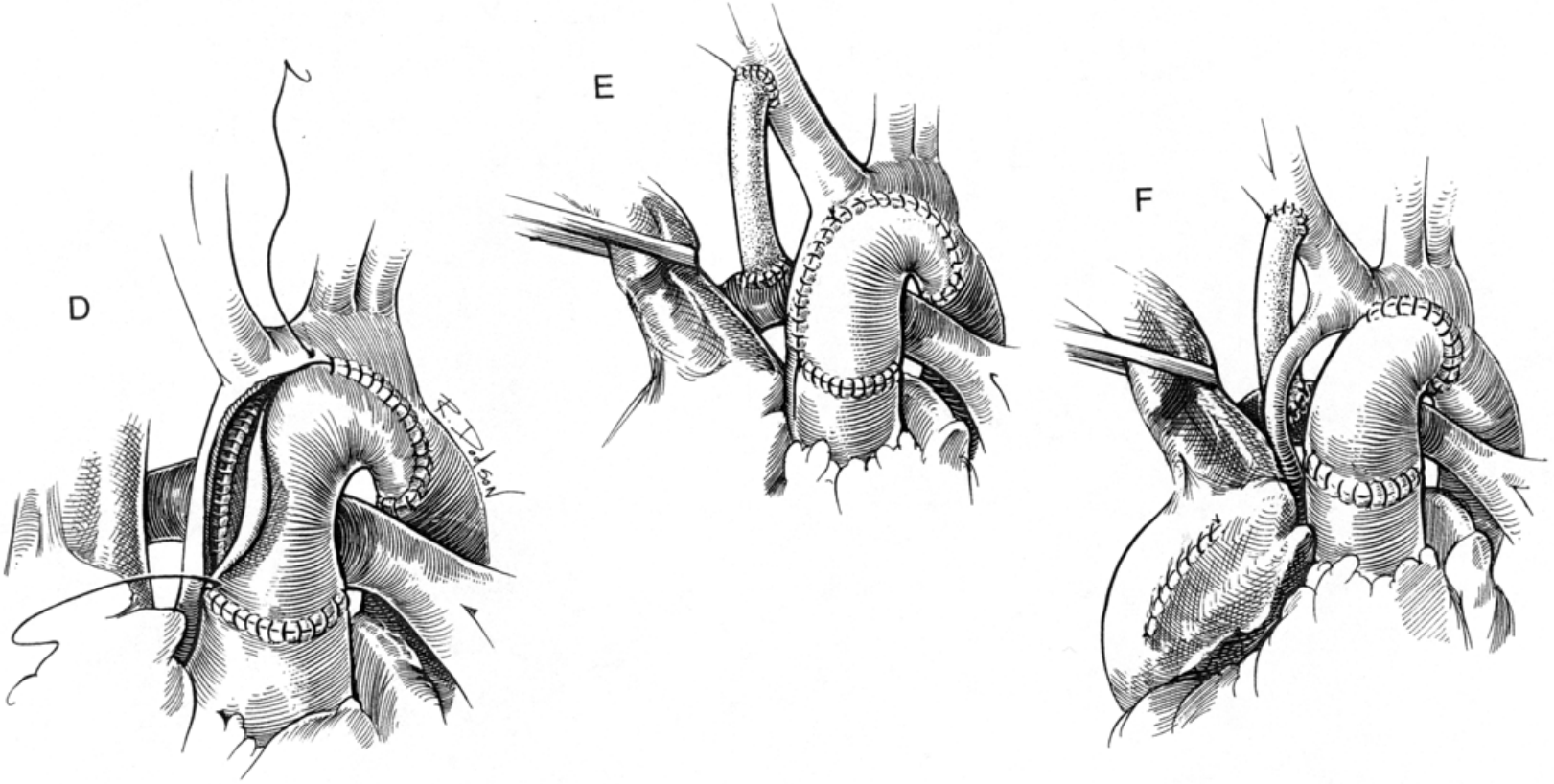
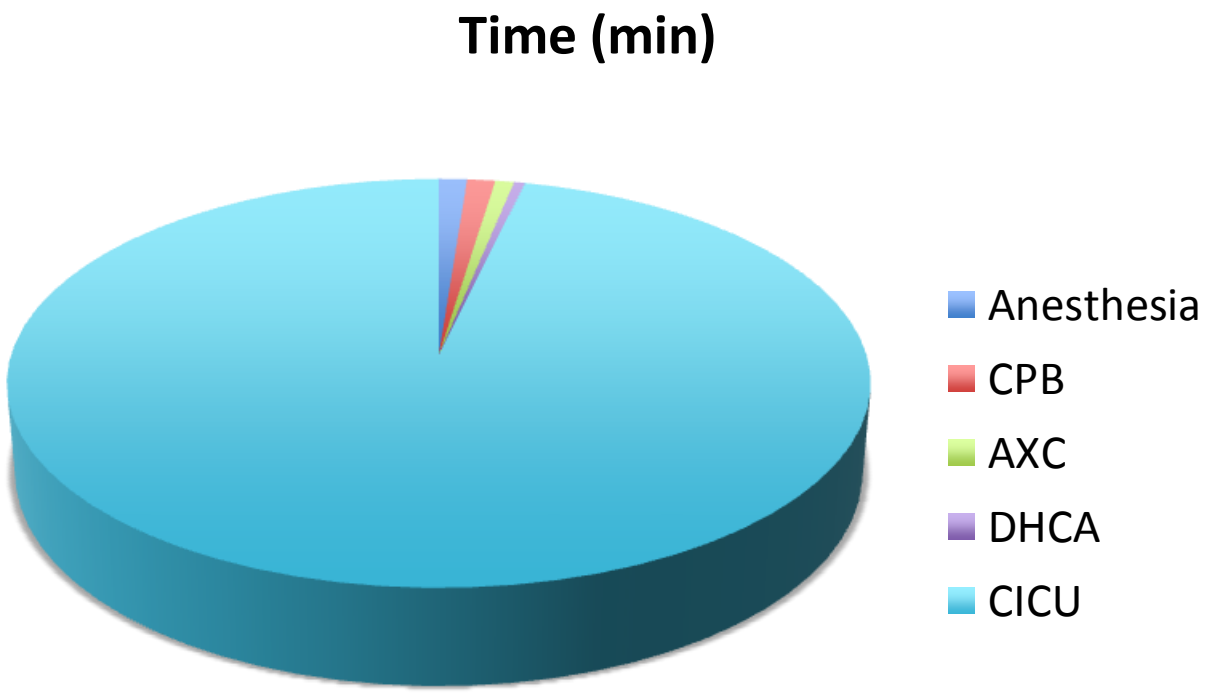


Are surgeons to blame for everything?



Neurodevelopmental (Early and Latent) Outcomes →

Abnormal Brain at Birth	Infancy	Pre-School	Middle School	Adolescence-Transition to ACHD
↓ head circumference	Seizures (cortex)	Delayed motor skills	Behavior problems	Depression and behavior problems
Structural abnormalities	↑ PVL (white matter)	Delayed language	Inattention/Hyperactivity	Inattention/hyperactivity
PVL	Delayed motor skills	Microcephaly	↓ Handwriting	↓ Visual motor integration
CNS immaturity			↓ Visual motor integration	↓ Planning and executive function

Causes of adverse neurodevelopmental outcomes: Multifactorial, interactive, and ongoing

Fetus → Birth → Surgery → ICU → Stepdown → → → Home → → → → → →

↓ Substrate delivery	Anesthesia	Early Modifiers	Late Modifiers
↓ Oxygen delivery	Opiates	Genetic Polymorphisms	Hypoxemia
↑↓ Cerebral resistance	Benzodiazepines	Alterations in CBF	Reoperations
Placental abnormalities	CPB	Hypoxemia, hypocarbia, hypotension	Socioeconomic Status
Genetic syndromes	Hypothermia	Hyperthermia	PTSD, maternal depression
Delayed diagnosis	Circulatory Arrest	Seizures Stroke	Poor nutrition

Preoperative Modifiers

Low Cerebral Blood Flow

Low Cerebral O_2 Content

ICU Morbidity (emboli, fever, etc.)

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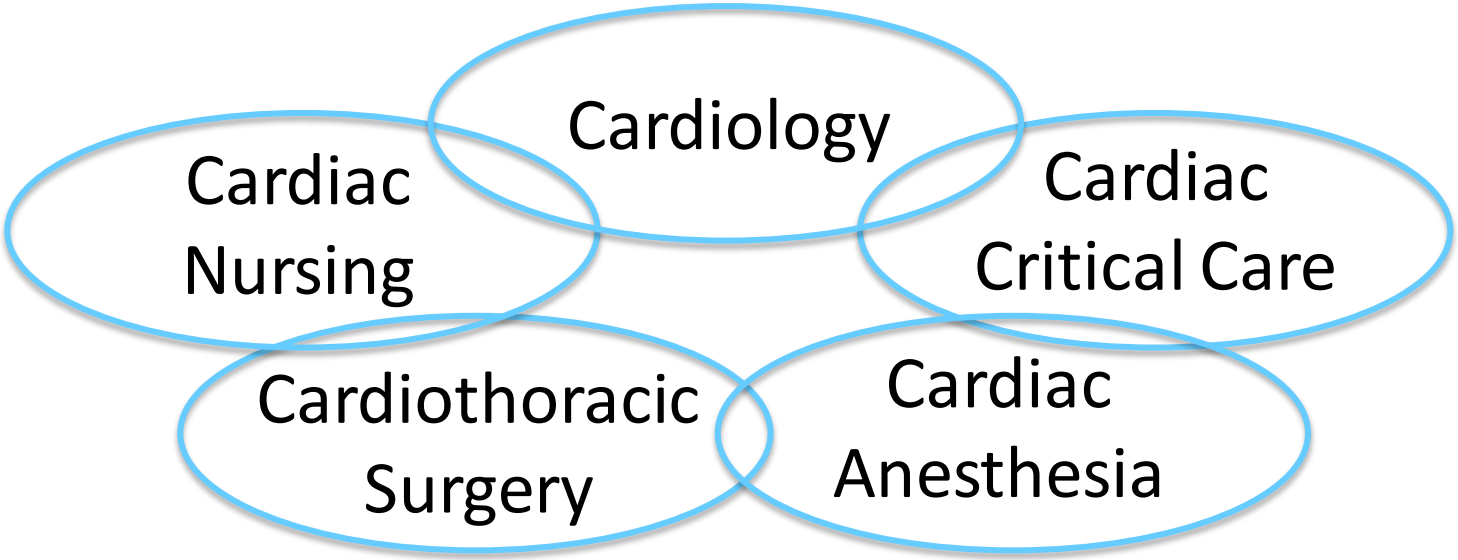
Preoperative Modifiers

Low Cerebral Blood Flow

Low Cerebral O_2 Content

ICU Morbidity (emboli, fever, etc.)

Collaborative Model of Care



What’s next

- precision therapies guided by genetics
- new and nano technology introduced drugs, devices, and materials
- robotic manipulations

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What tools are in place

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- sequencing and bioinformatic tools
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- ontologies that speak to each other

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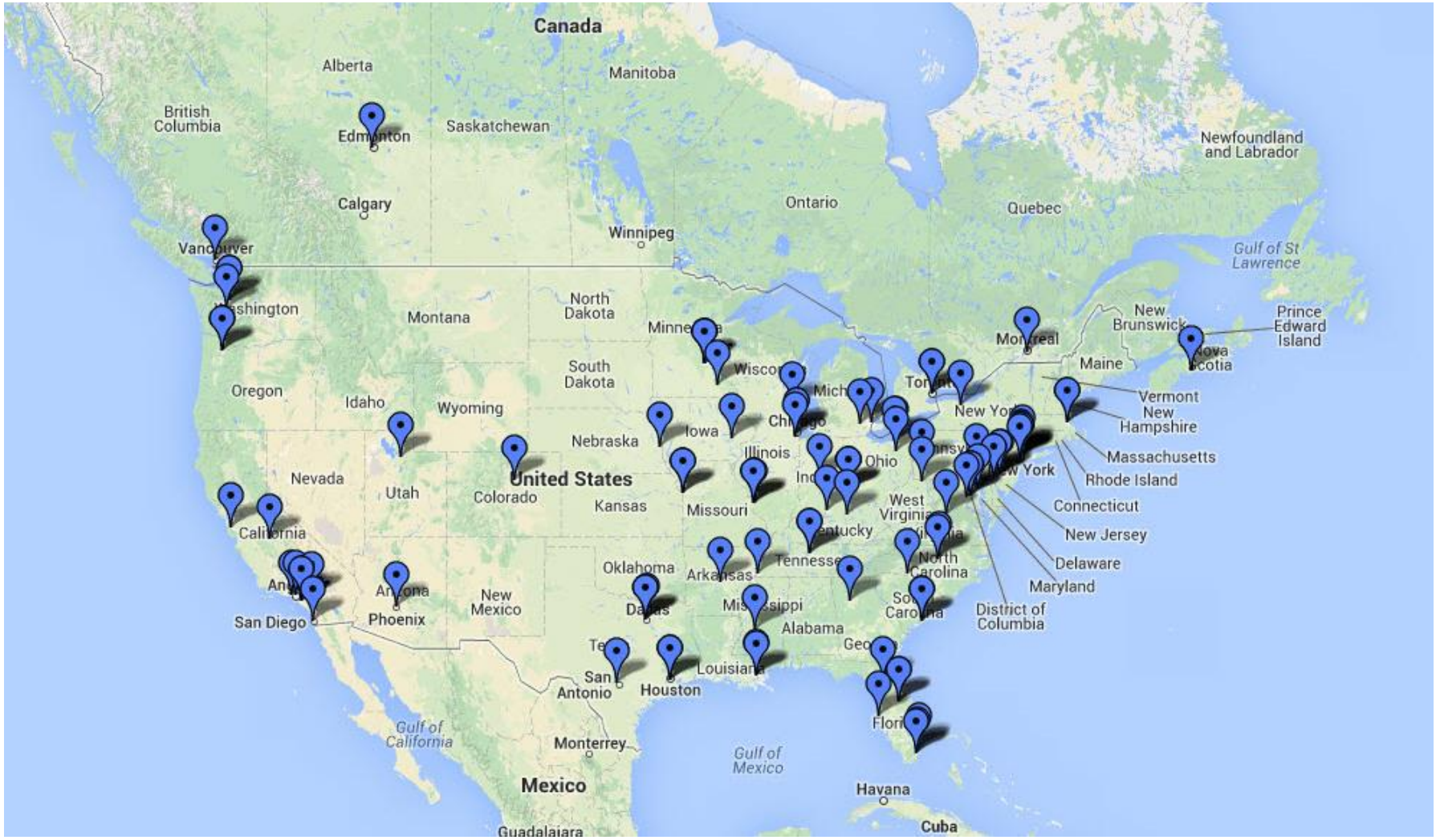
How do we get many thousands of samples to analyze?

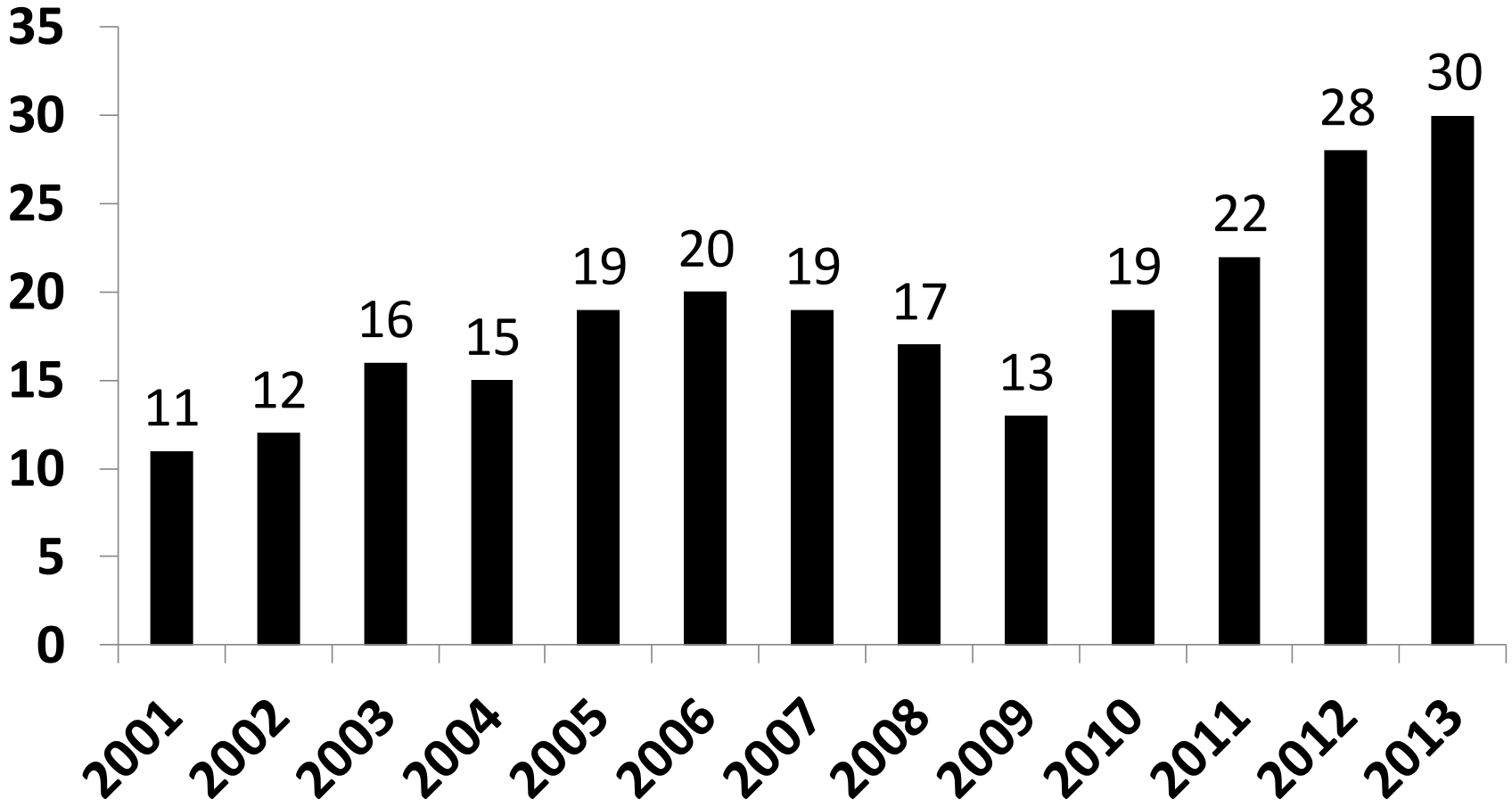
- I have thousands of DNA, hundreds of tissue, and tens of stem cells lines- not enough

- Collaboration to get the rest
  - single investigators
  - institutional BioBanks
  - larger initiatives

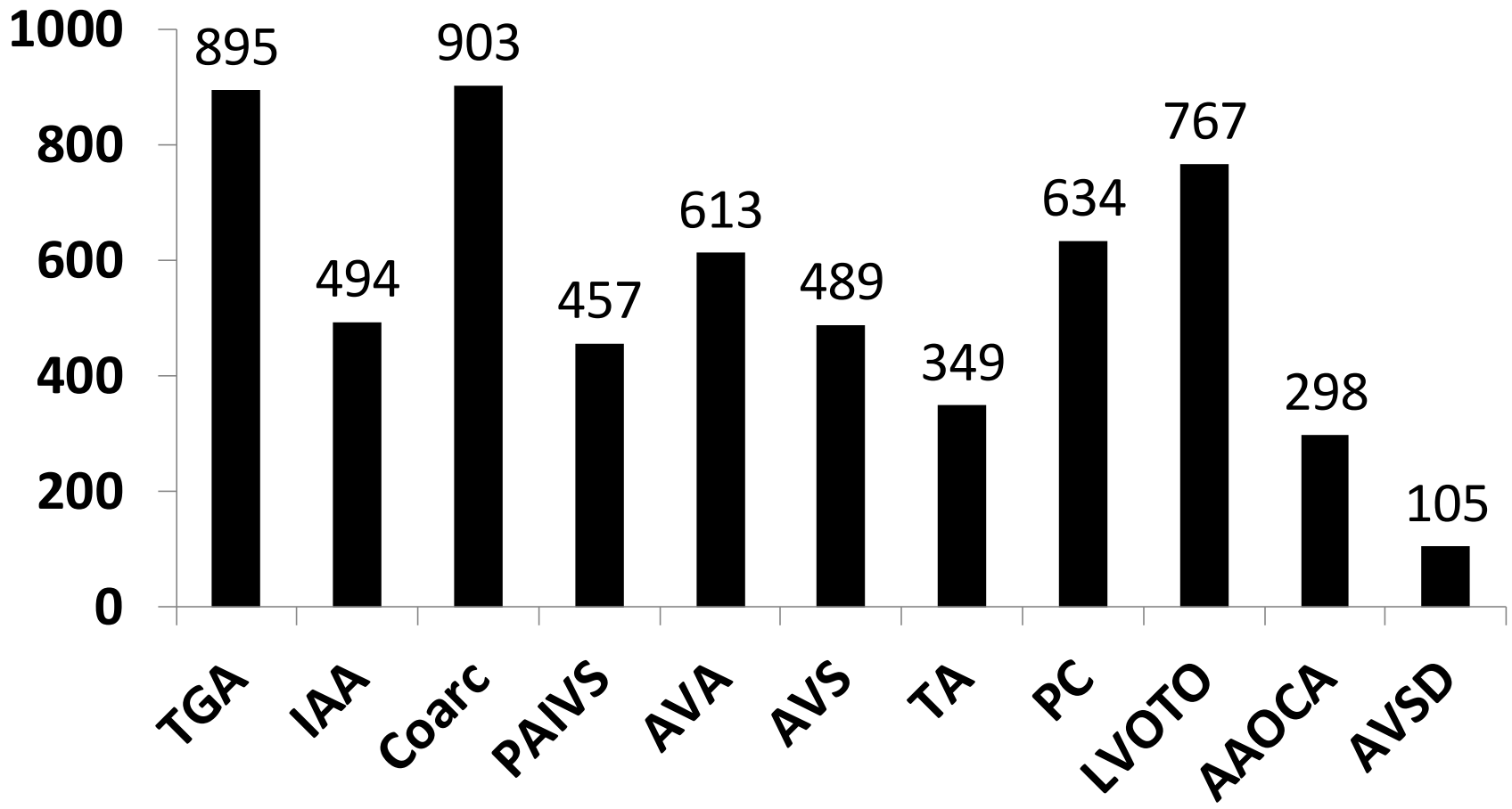
CHSS collaborative sites



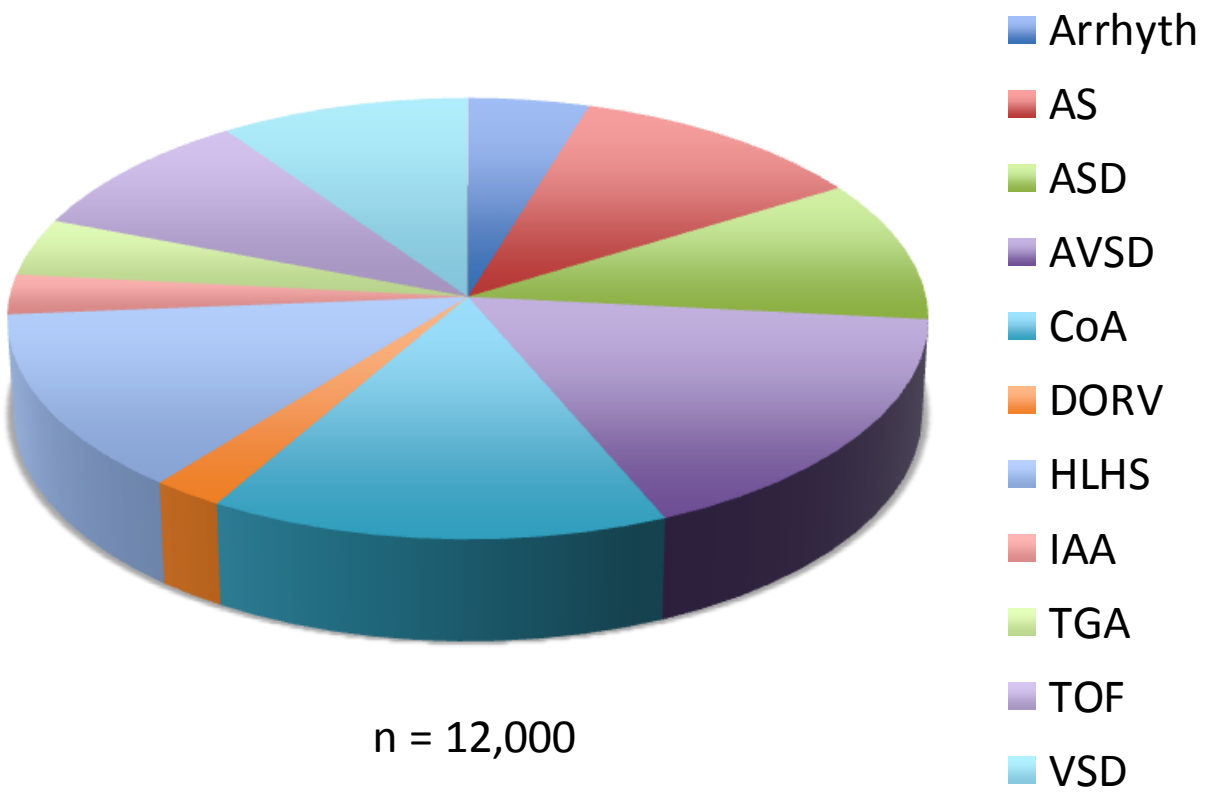
CHSS enrolling institutions



CHSS study enrollment



Samples by diagnosis



n = 12,000

What tools are in place

- patients and clinical data
- sequencing and bioinformatic tools
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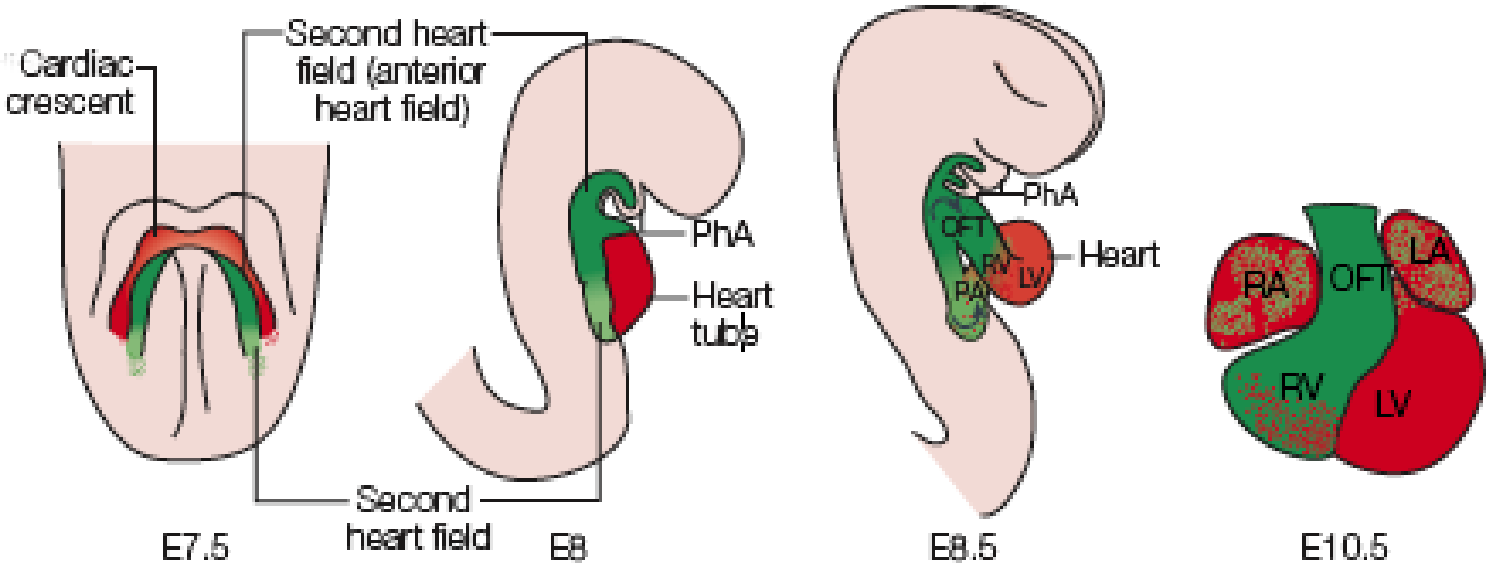
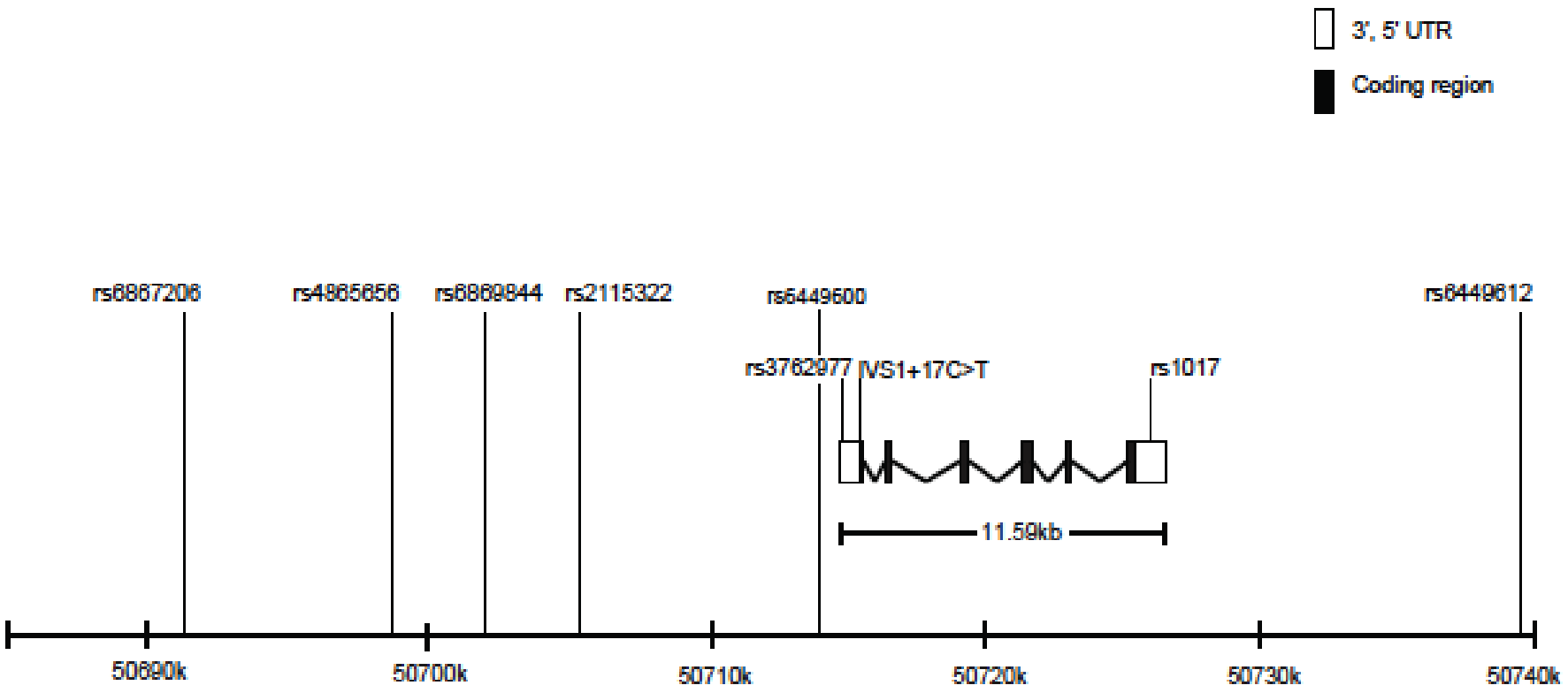
- ontologies that speak to each other

Turn to development for answers

- Fish- transgenic zebrafish
- Mice- gene-targeted mice
- Human- genome sequencing and iPSC production



Chr 5 variation in the *ISL1* region



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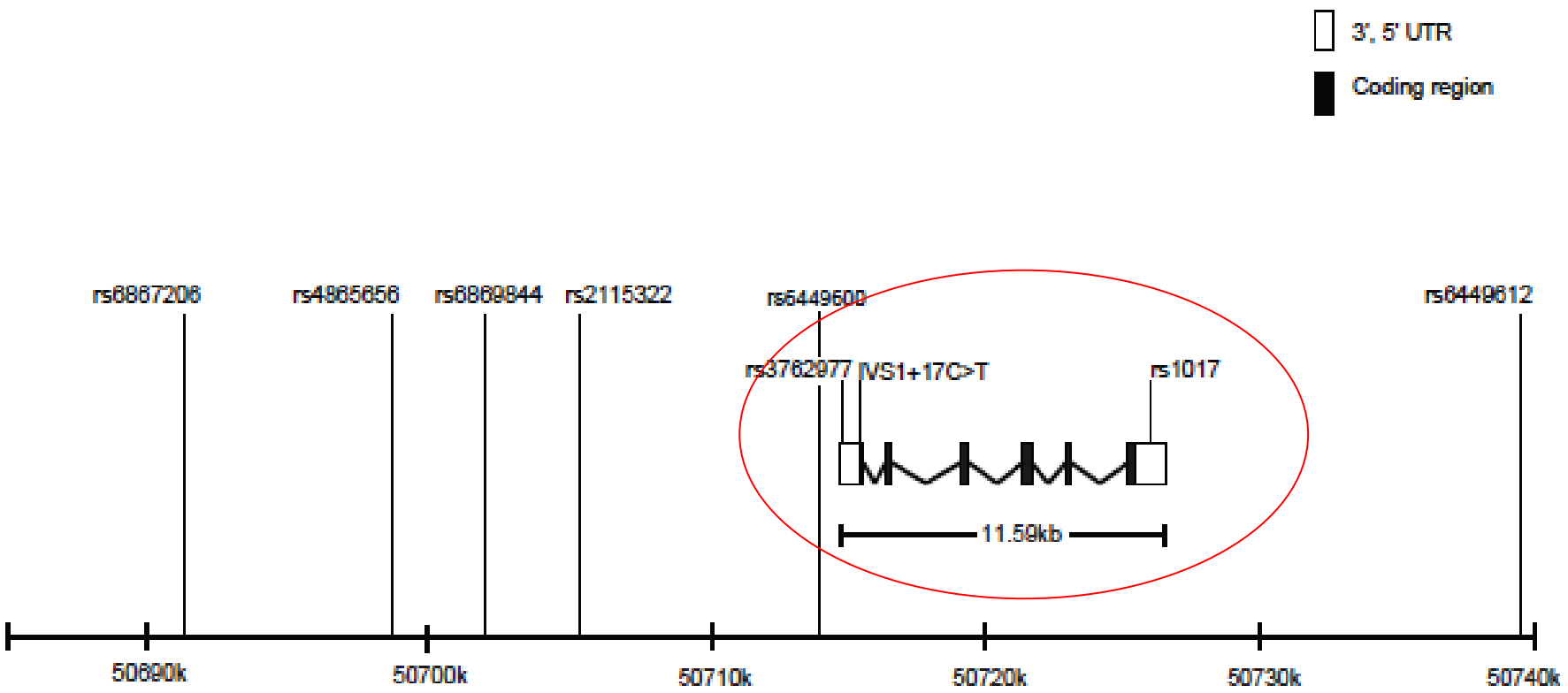
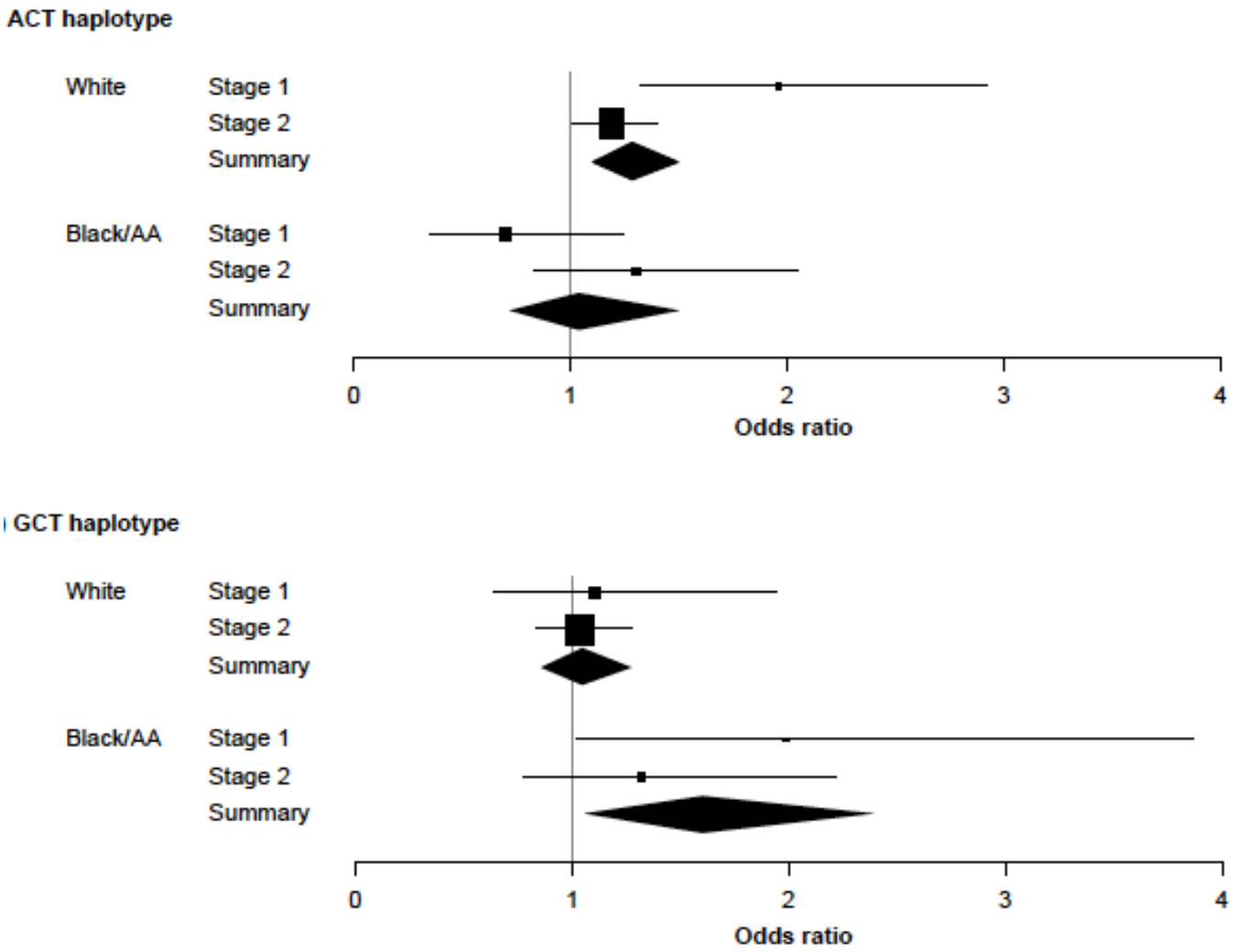
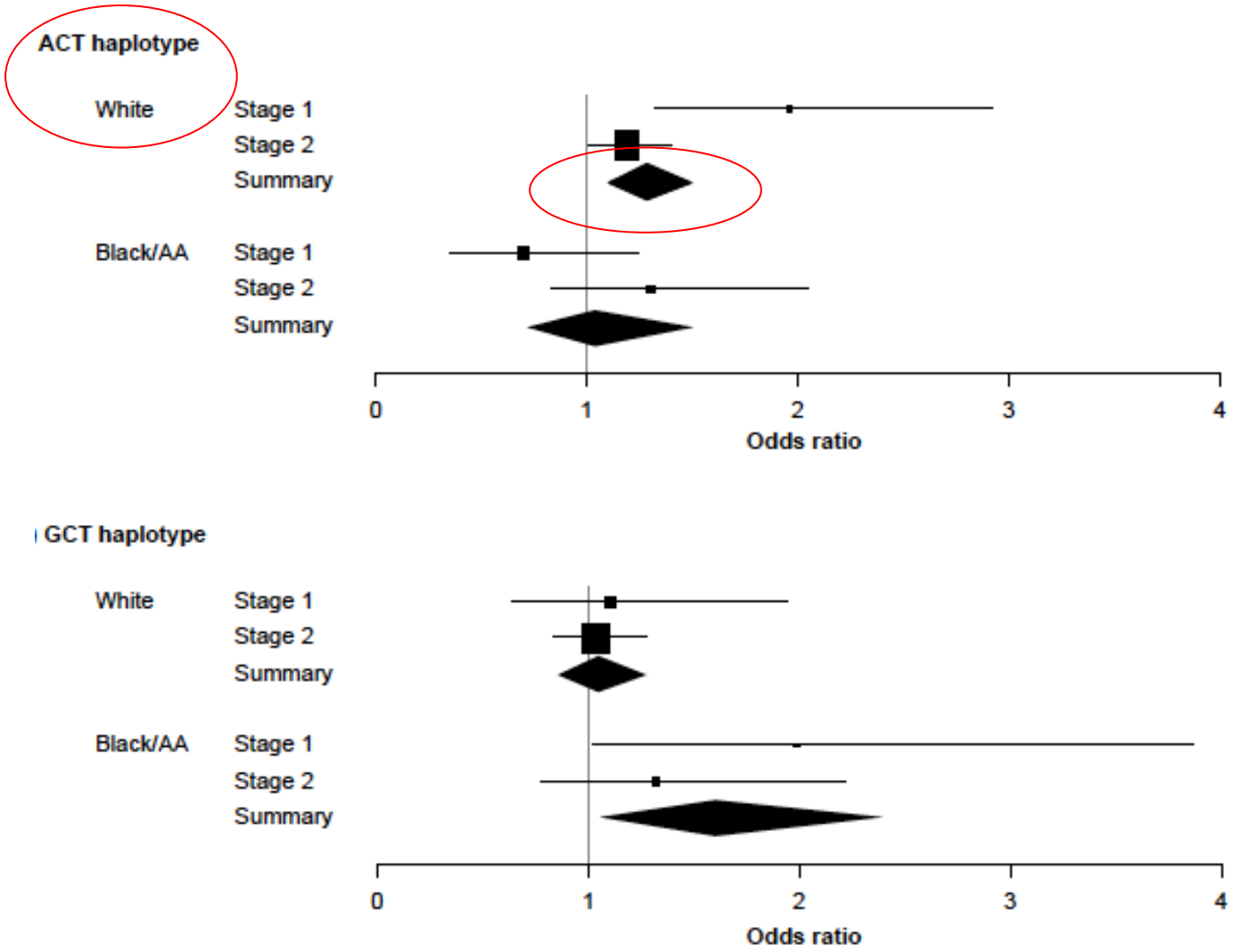


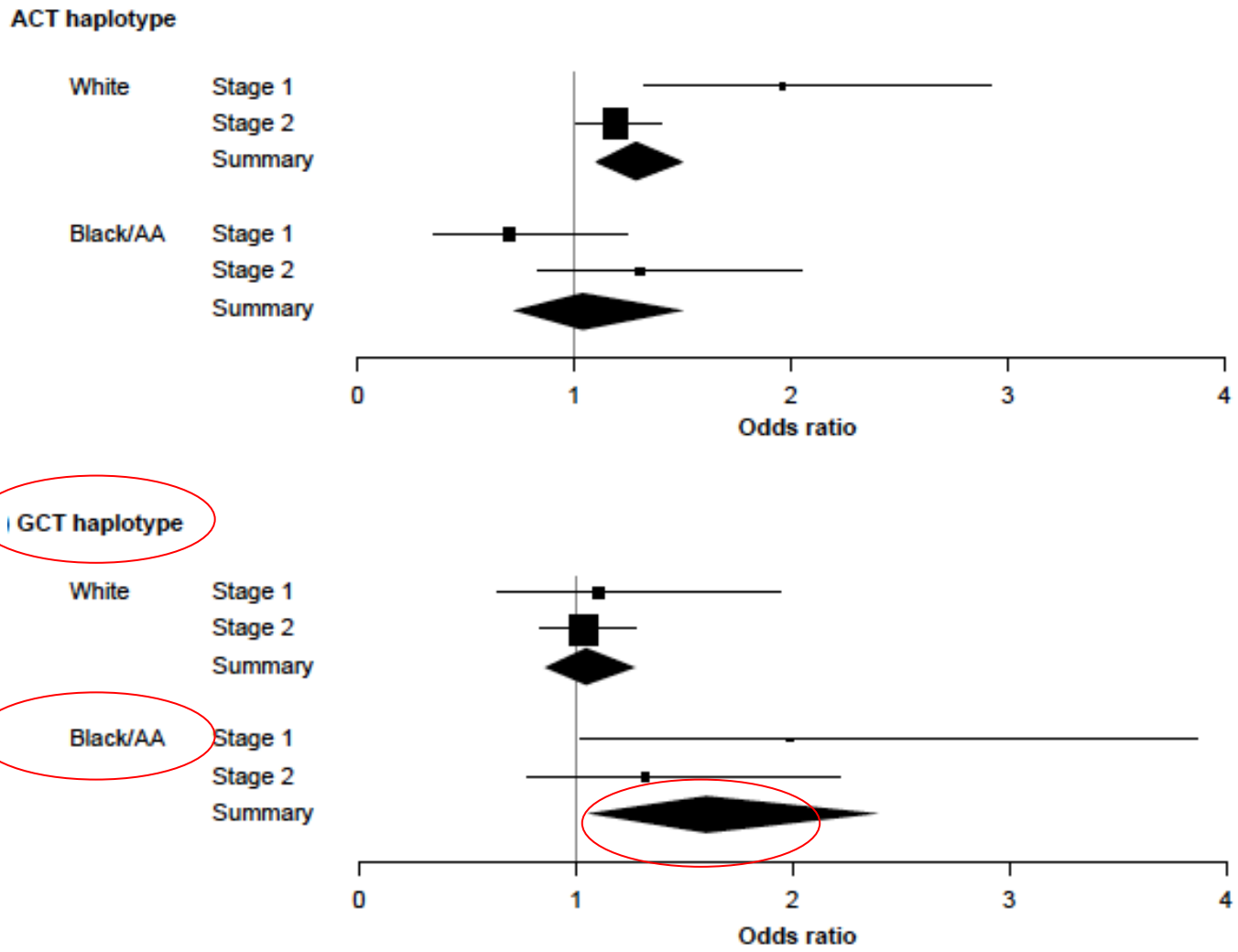
ISL1 risk by ethnicity



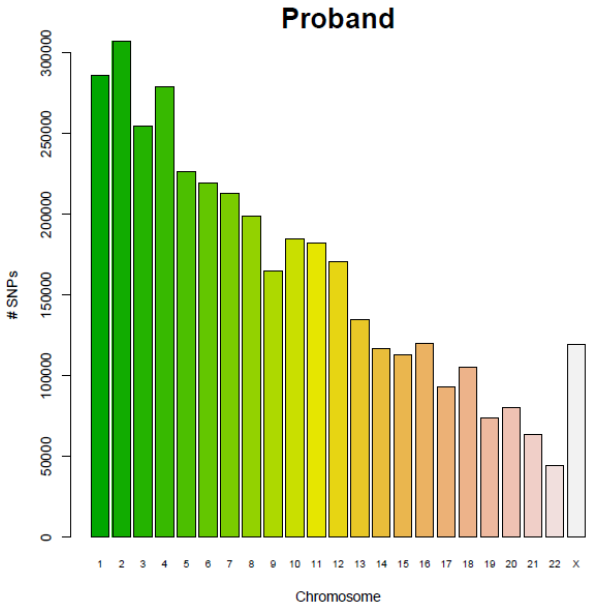
ISL1 risk by ethnicity



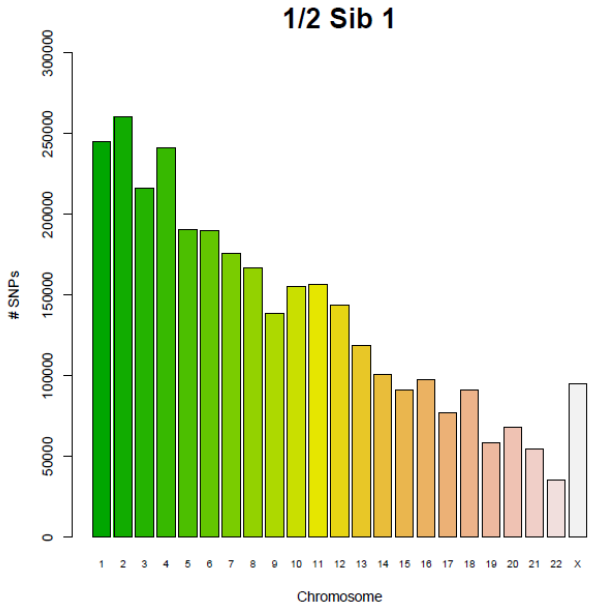
ISL1 risk by ethnicity



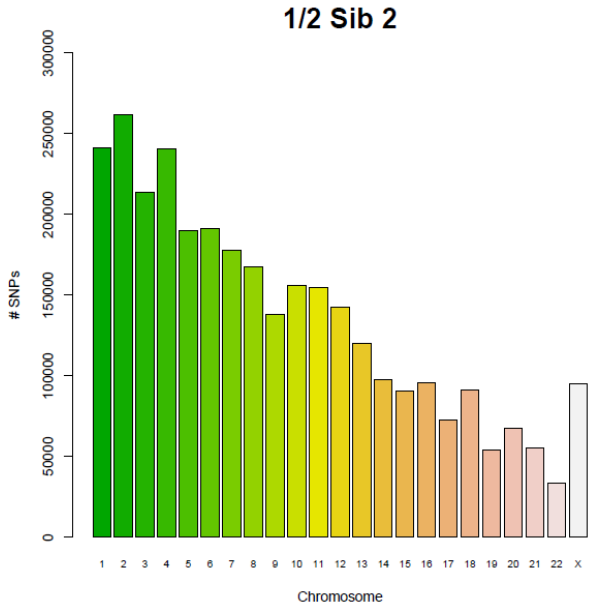
Total # SNPs by chromosome



Total=3,754,214



Total=3,169,270



Total=3,147,463

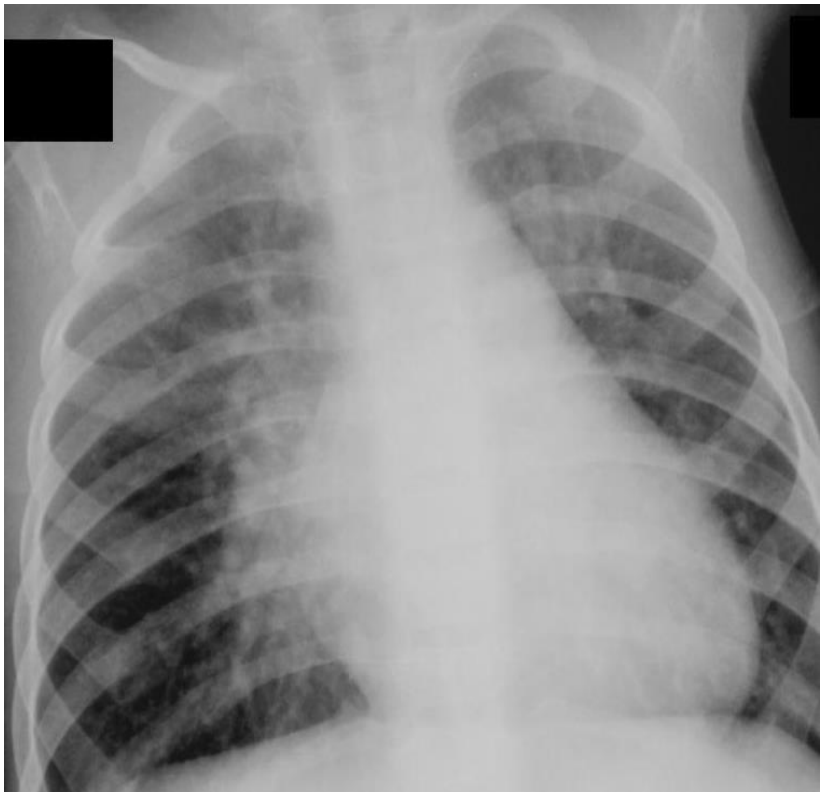
What's next

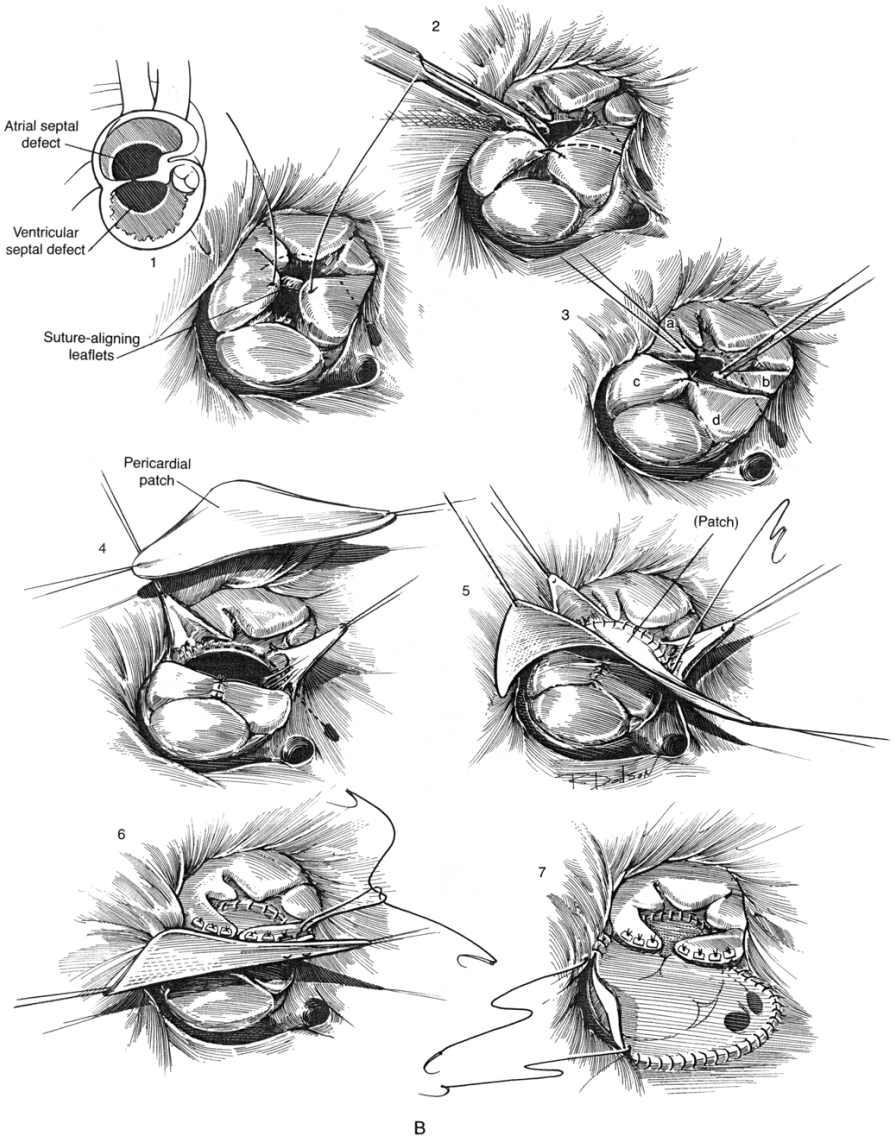
- precision therapies guided by genetics
- new and nano technology introduced drugs, devices, and materials
- robotic manipulations

2 y.o. TOF/AVC

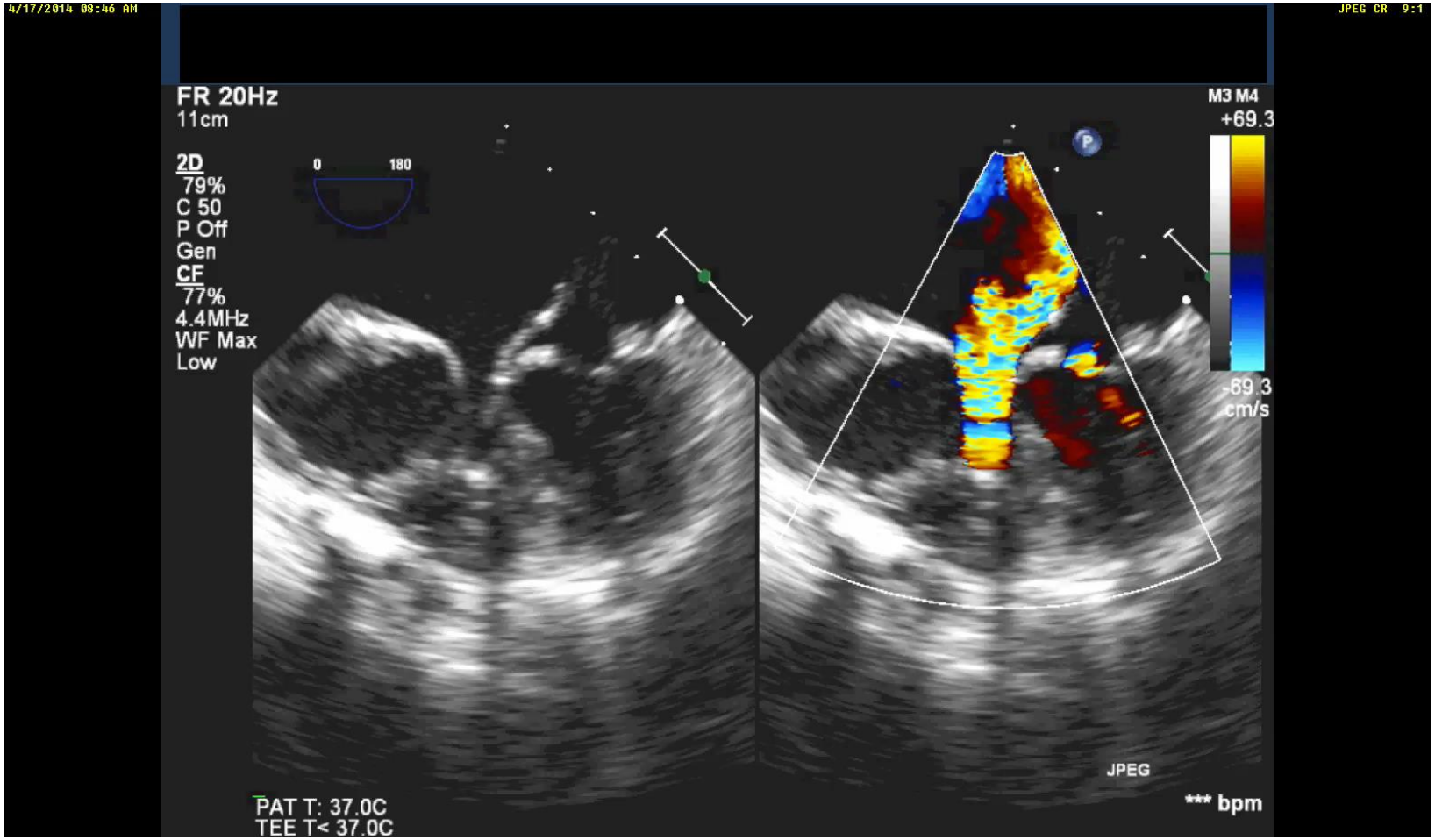
- 2 y.o. female with transitional AVC, dysplastic RAVV, and PV stenosis.
- primary repair in infancy
- secondary repair at 1 year with RAVV repair and RV-PA conduit.
- now with PA stenosis and severe RAVV regurgitation

Complete common AV canal

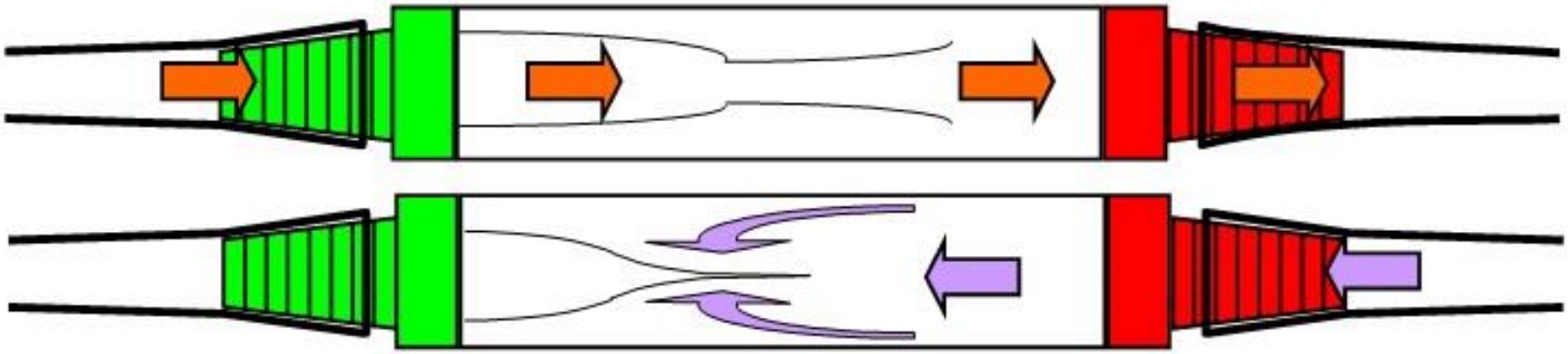




Native valve function- pre



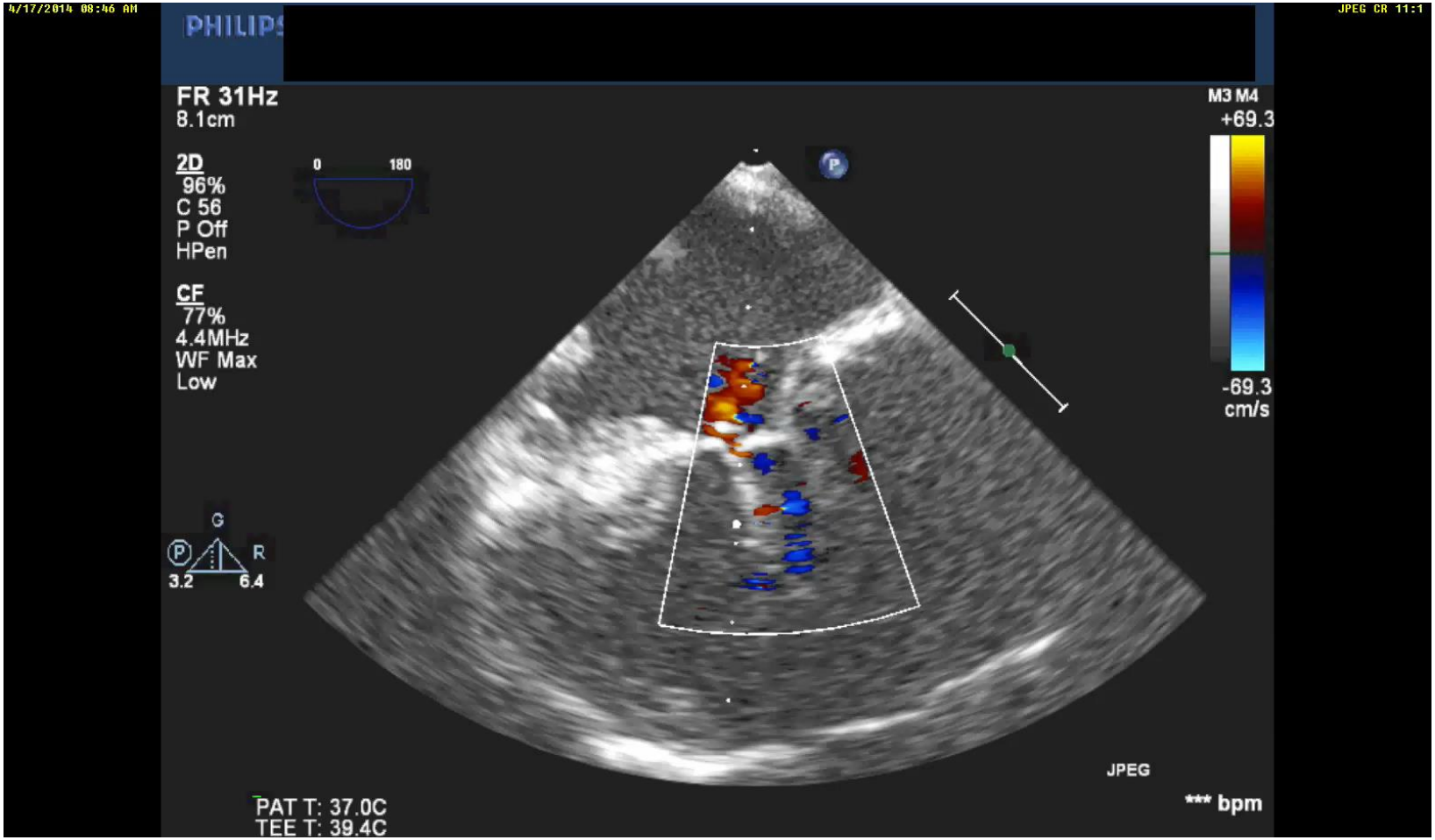
Heimlich valve principal



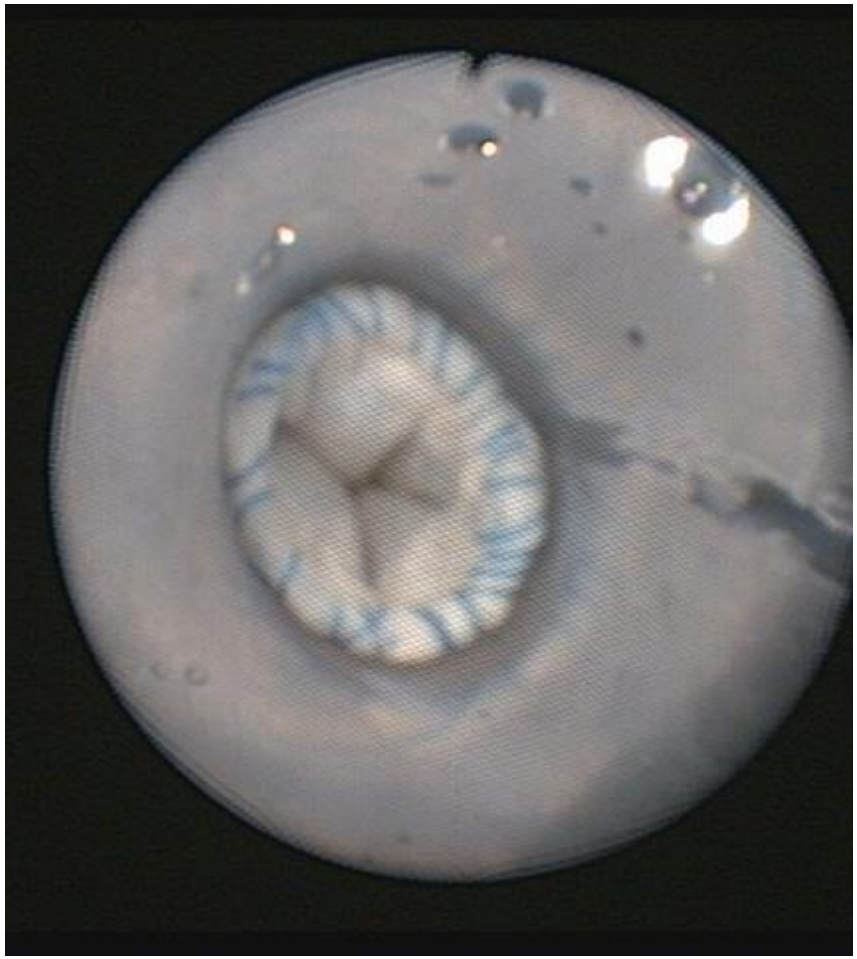
ECM TV creation

- completed cylinder valve
- ends are tacked to ventricular wall
- other cylindrical end is sewed to annulus

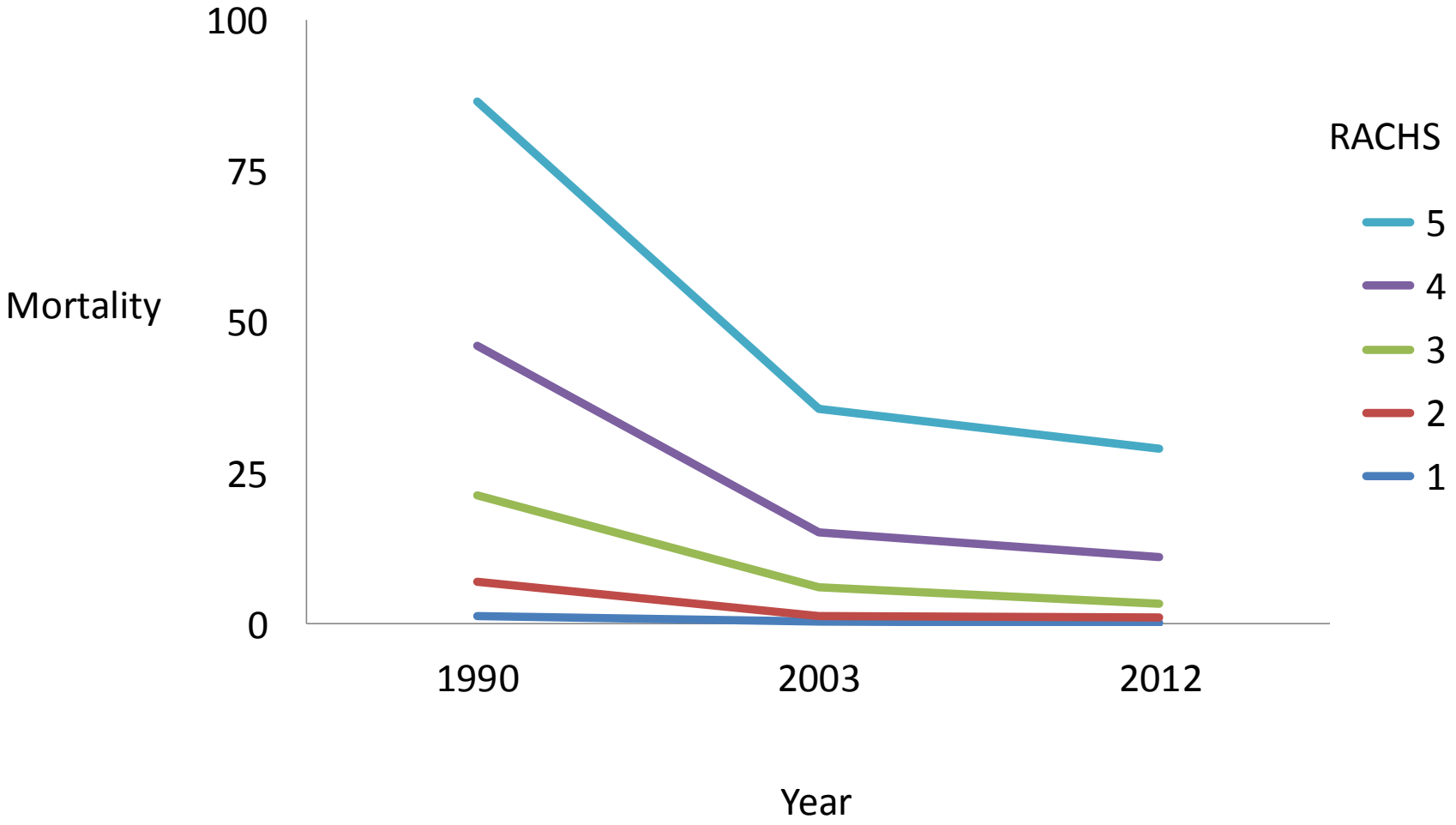
ECM TV function- post



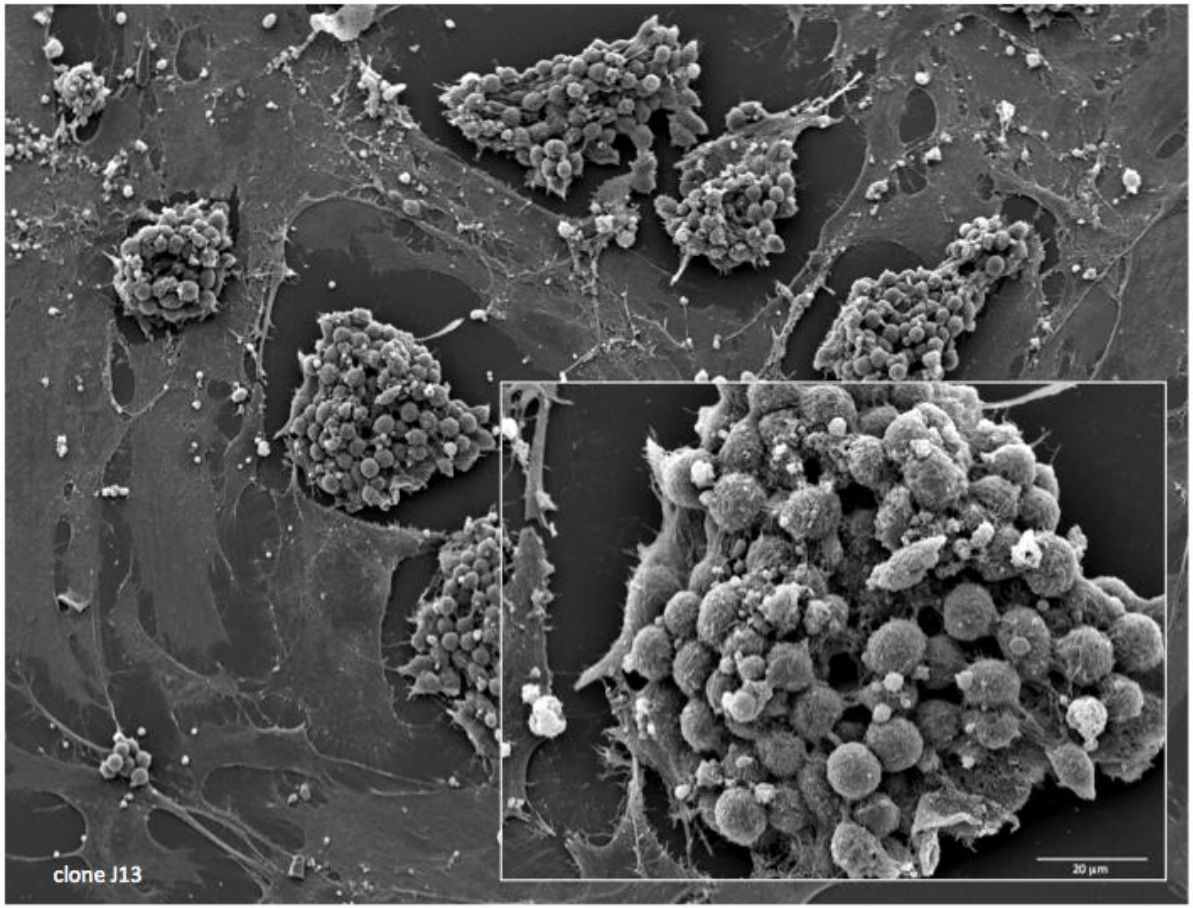
In vitro images

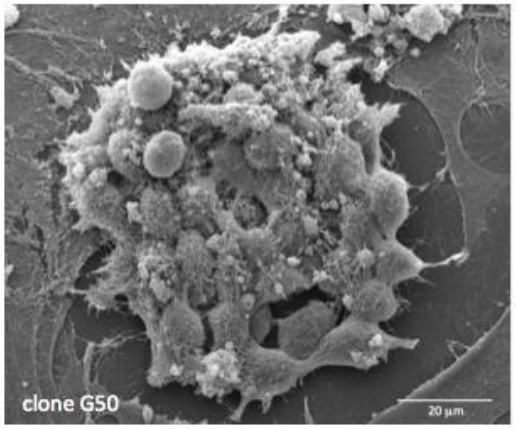


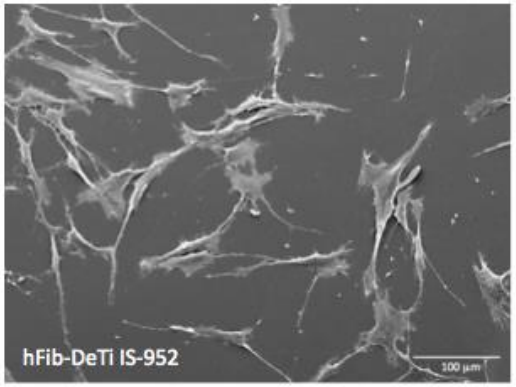
Risk in Congenital Heart Surgery: Chronological improvement



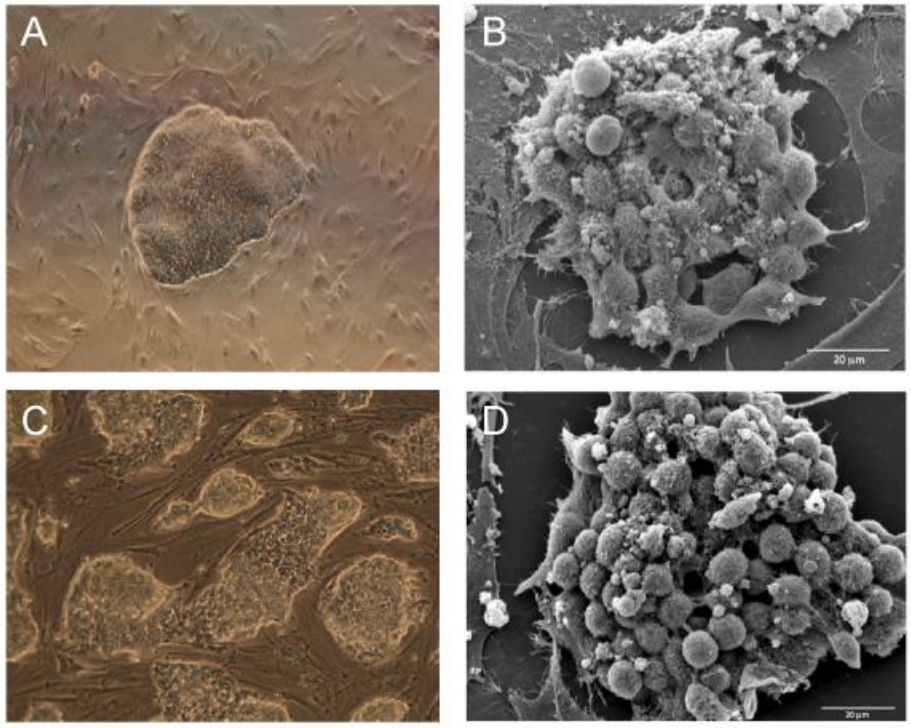
Generation of human iPS cells of patient specific tissue







Patient-specific cellular reprogramming in CHD

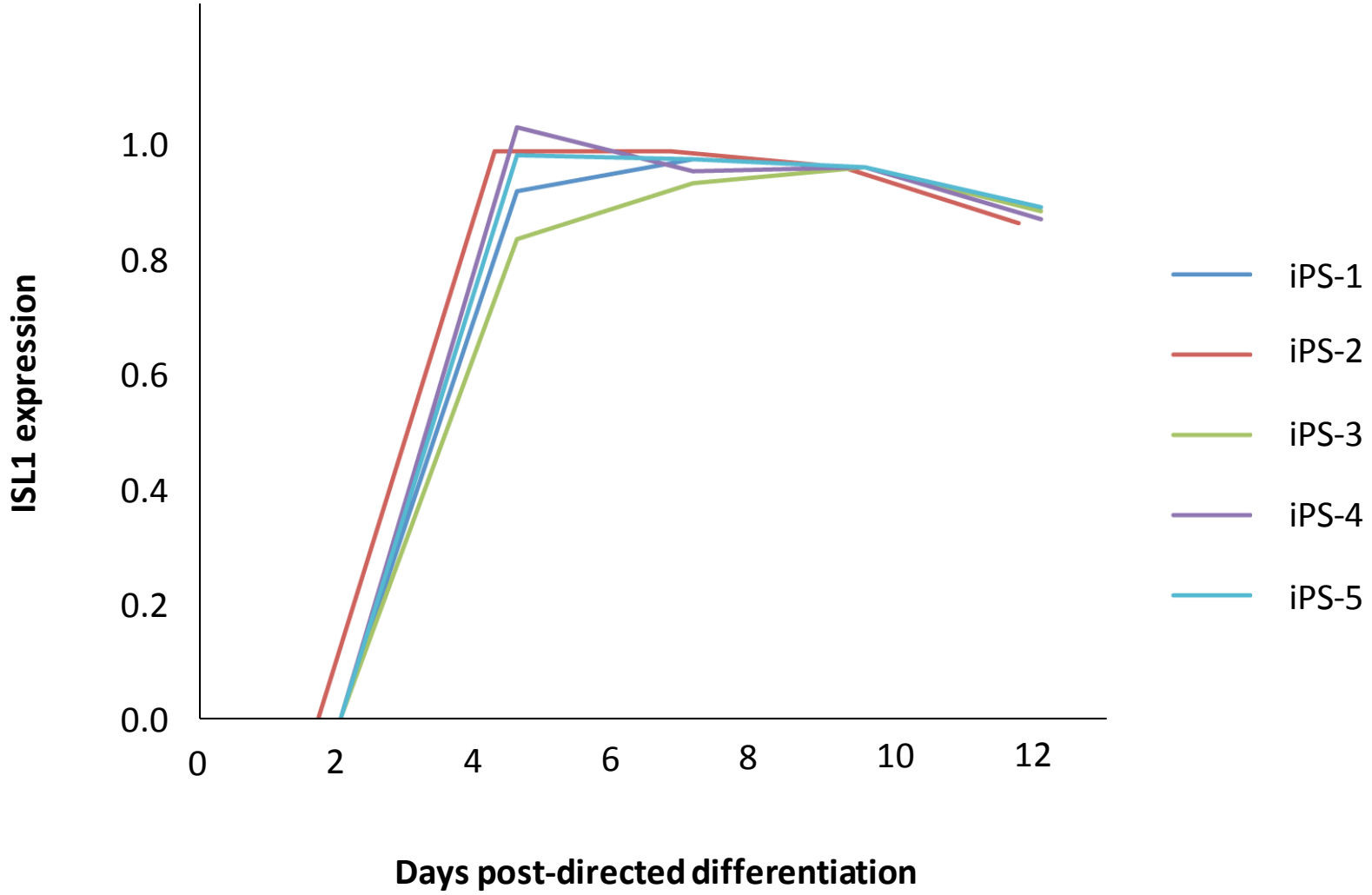


-11 lines of AF: gest age 3@19, 3@20, 1@22, 1@25, 1@32, 1@33 weeks
- average reprogramming time with clonal selection = 3 weeks
- creation of >100 stable iPS cell lines

Reprogramming using amniocentesis-derived fibroblasts

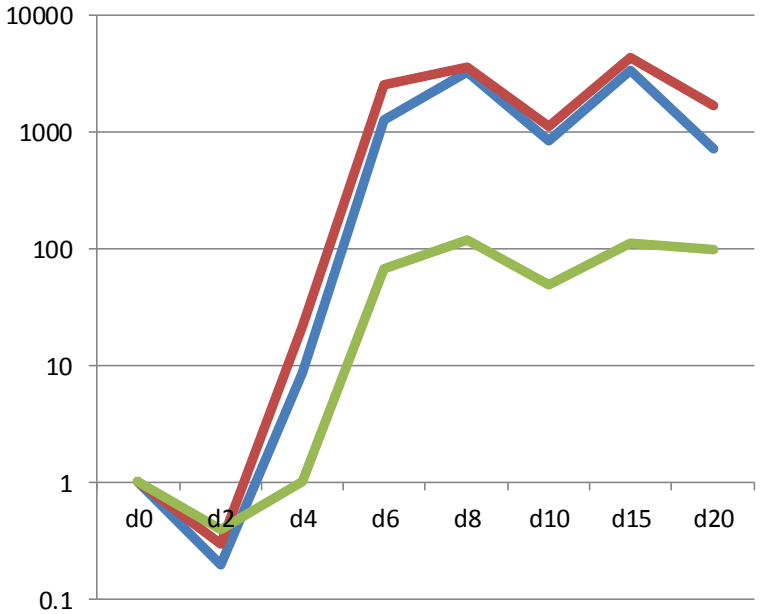
Experimental Time (Gest. Age)	**Procedure**
0 (14-20 weeks)	Amniocentesis
1 day (14-20 weeks)	Purification of amniotic fluid fibroblasts
1 week (15-21 weeks)	Expansion of fibroblasts
2 weeks (17-23 weeks)	Transduction of fibroblasts (4XF/miR)
1 week (18-24 weeks)	Selection of iPSC clones
1 week (19-25 weeks)	Screen iPSC clones
3 weeks (22-28 weeks)	Expansion iPSC clones
2-6 weeks (24-32 weeks)	Directed differentiation
4-8 weeks (28-40 weeks)	Assay of differentiated cell types

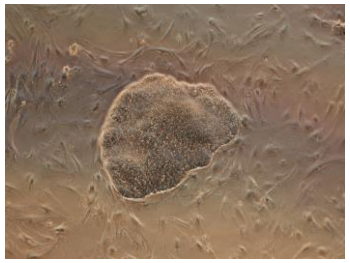
Cardiac differentiation of human iPS cells



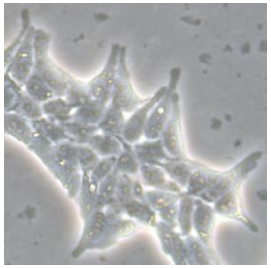
Neuronal differentiation

Expanded iPS clones of two different patient with congenital heart disease and hES as a control (beta III tubulin)





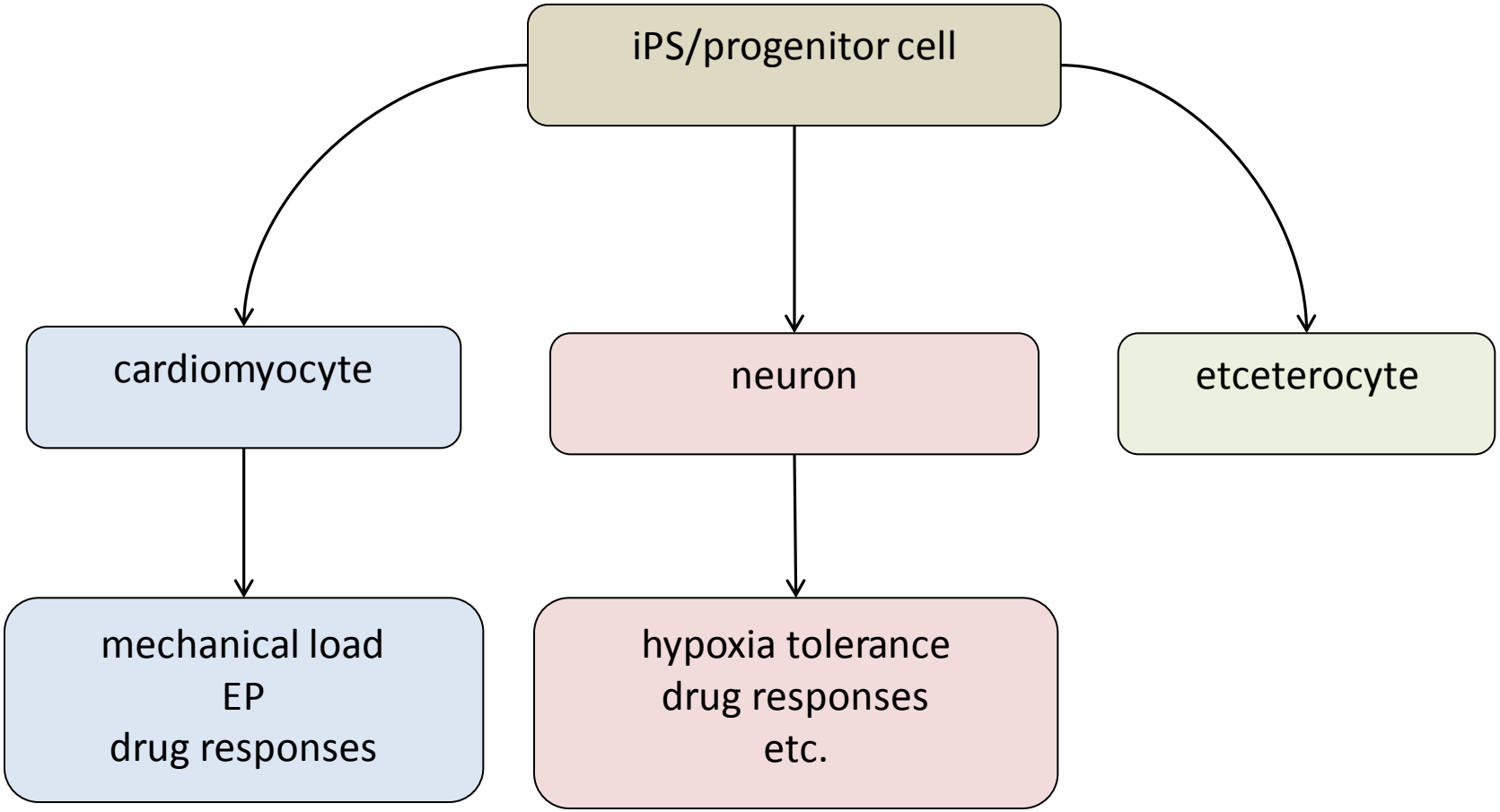
iPS
precursor



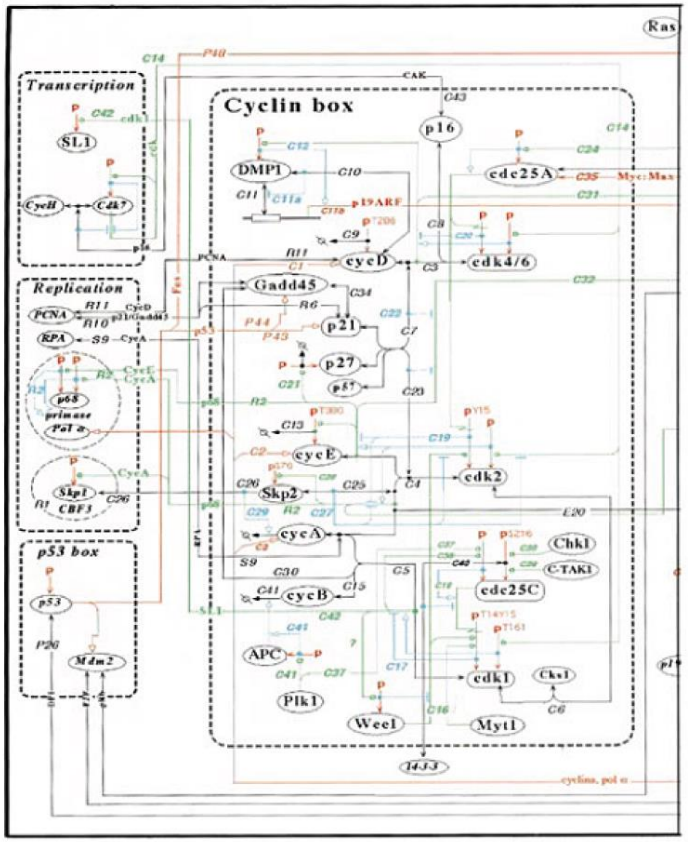
Neural
induction

Neural
differentiation

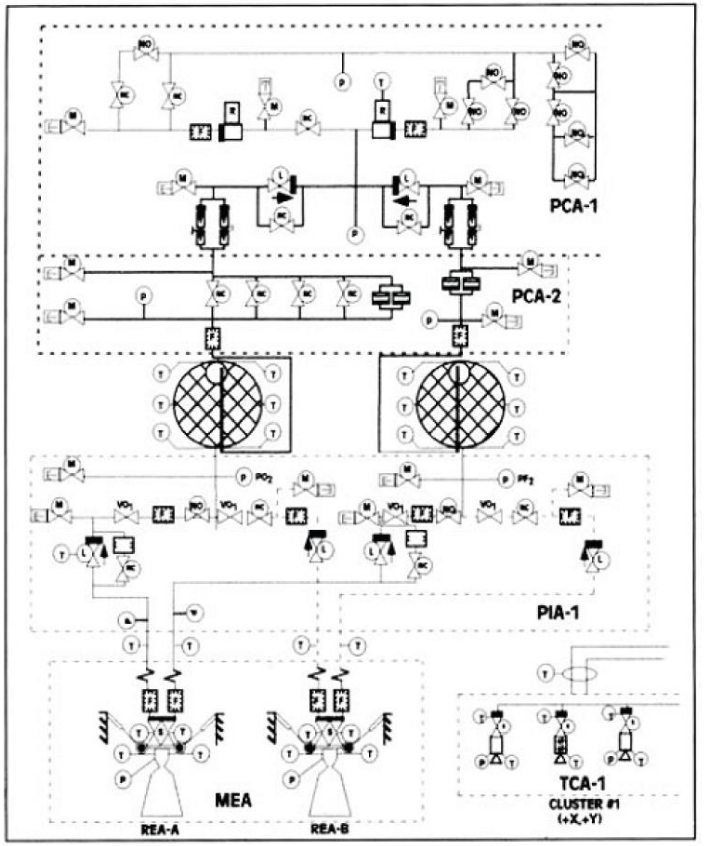
Directed differentiation of patient-specific iPS cells may eventually help predict responses



“This isn’t rocket science, it’s much harder” (A. Spiegel)



Portion of G1-S transition (Korn, 1999)



Portion of propulsion and altitude control, system from Cassini-Saturn mission (NASA)