

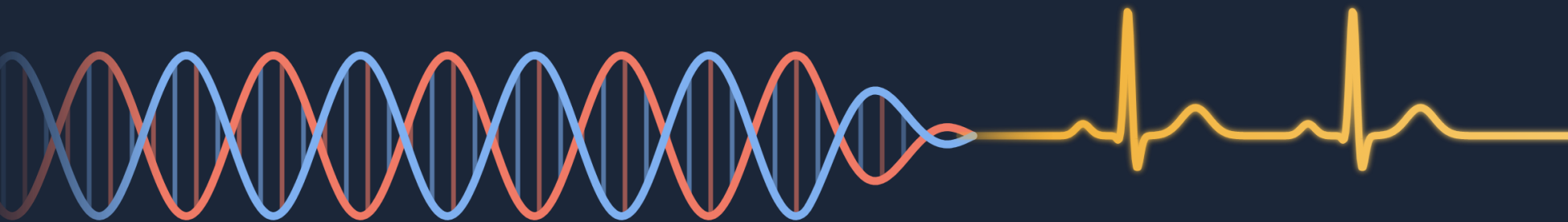
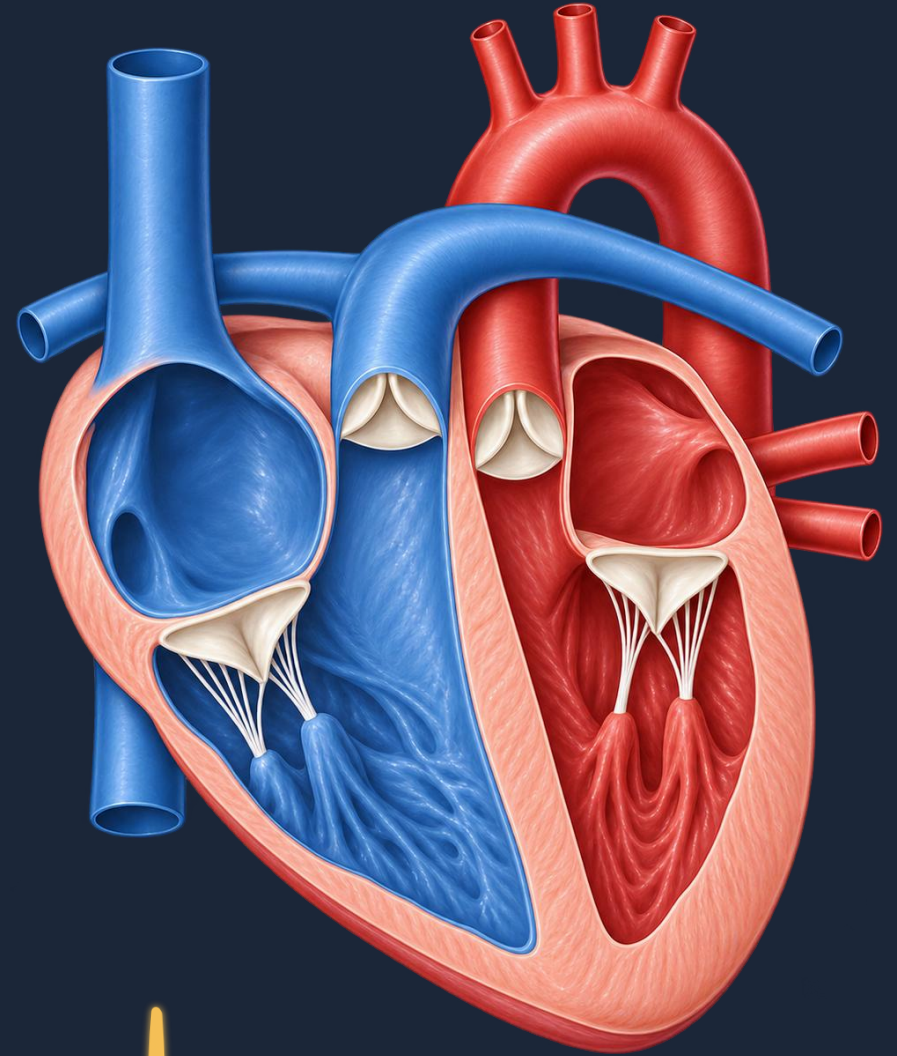
NOONAN SYNDROME ASSOCIATION CONFERENCE · 10 OCTOBER 2026

Noonan syndrome and the heart

What we know, what we do, and what comes next

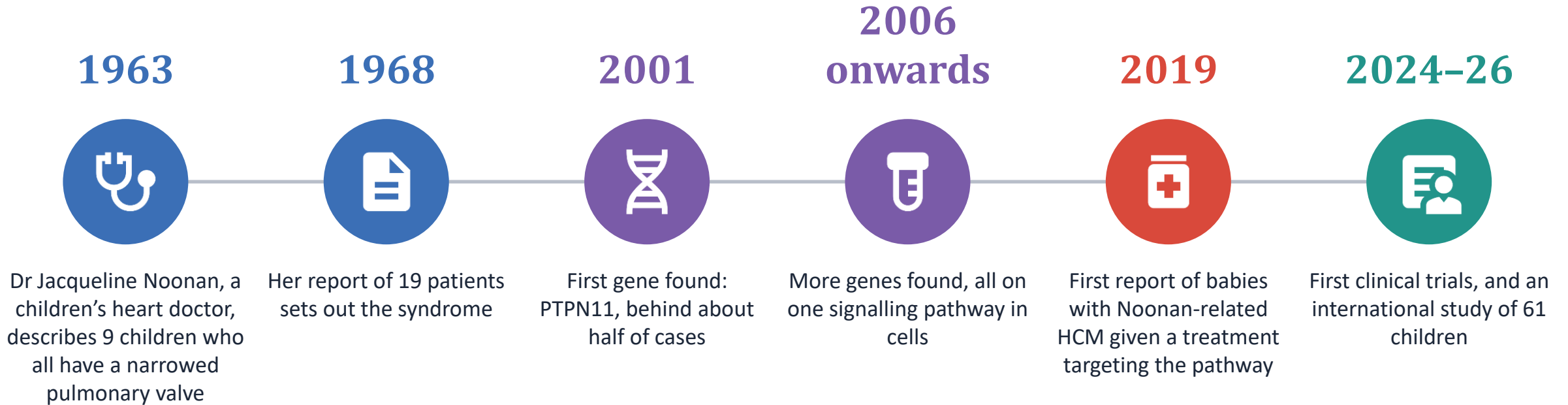
Dr Andrew Constantine

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Queen Elizabeth Hospital Birmingham



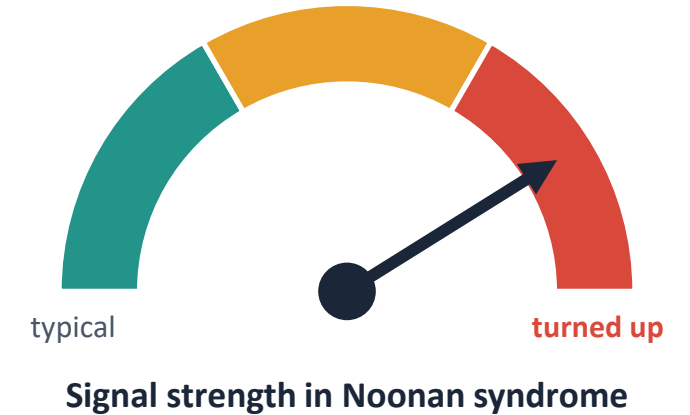
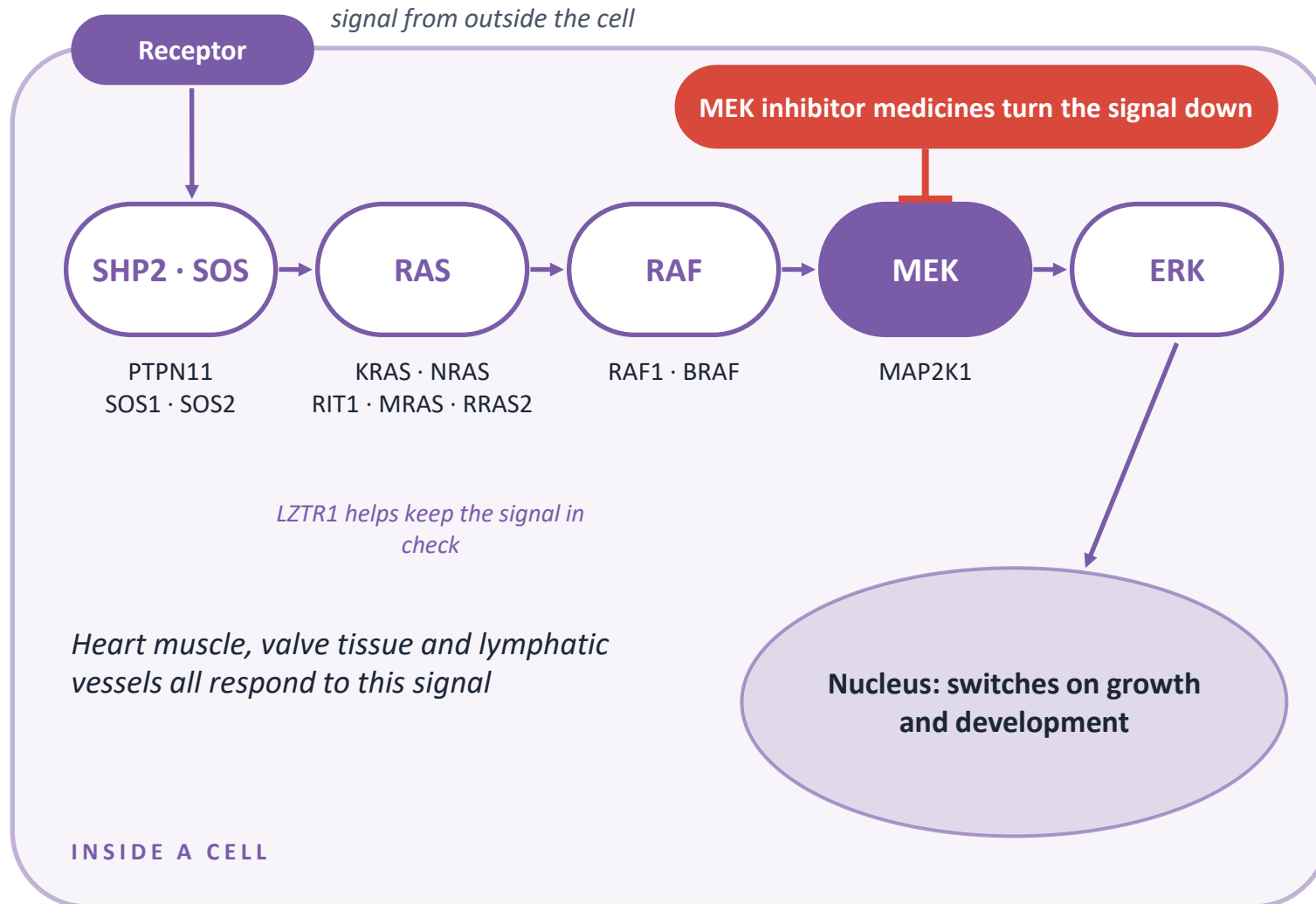
It began in a children's heart clinic

Sixty years on, the heart is still central to Noonan syndrome care



Jacqueline Noonan (1928–2020) helped write the heart guidance in the 2010 European (DYSCERNE) Noonan syndrome guideline

Why the heart? One cell signal, turned up



- Noonan genes affect a message pathway inside cells
- It helps tell cells, including heart cells, when to grow
- Different gene changes can affect the heart in different ways

Four parts of the heart to know about

1 Structure

Valves and walls that formed differently before birth

6 in 10

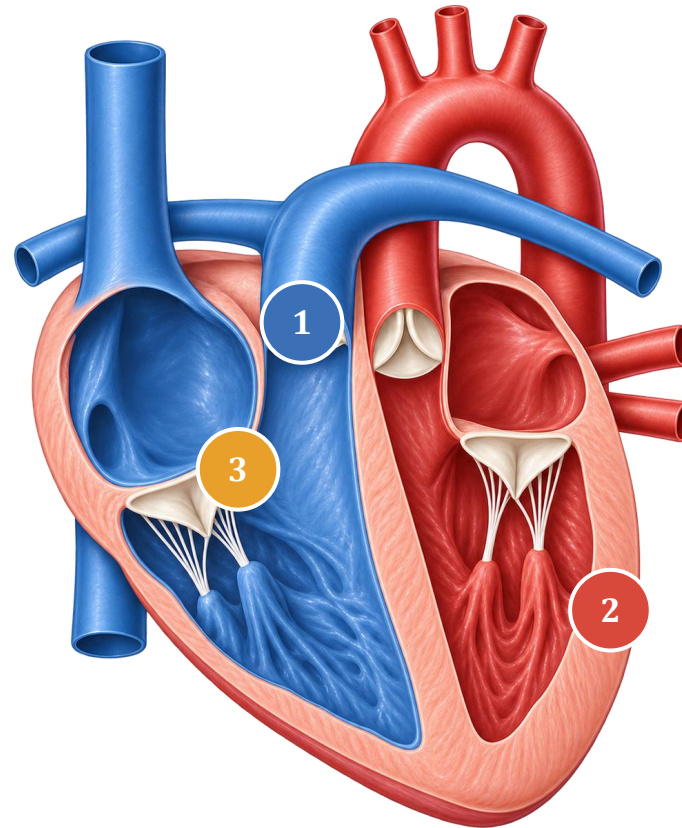
had pulmonary valve narrowing in one clinic study

3 Wiring

Heart rhythm and the ECG

1 in 2

have a characteristic ECG pattern



2 Muscle

Thickened heart muscle: hypertrophic cardiomyopathy (HCM)

1 in 5

people with Noonan syndrome

4 Check-ups

Follow-up when the heart is normal

For life

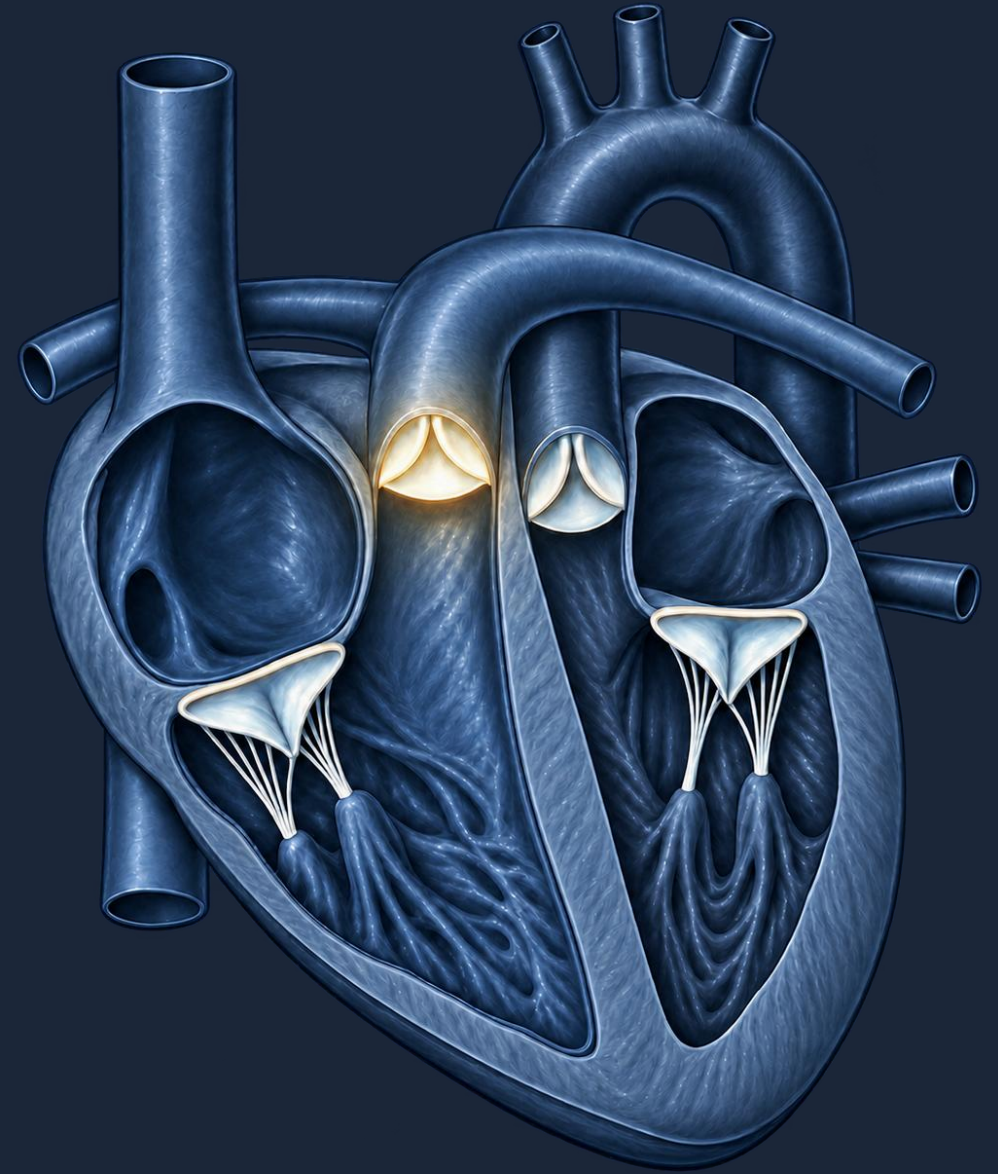
at least every 5 years for adults

1

Structure

Valves and walls: congenital heart disease

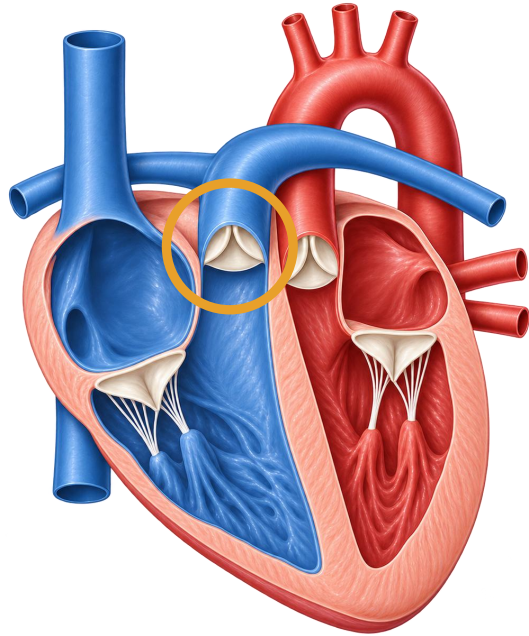
The pulmonary valve · treatment choices · other differences · our Birmingham data



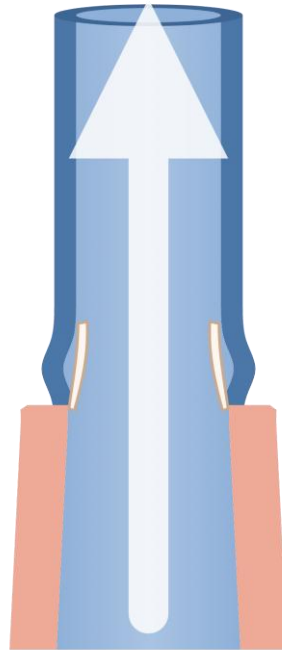
The pulmonary valve: a door to the lungs

1 · STRUCTURE

Pulmonary stenosis affected about 6 in 10 people with Noonan syndrome in one large clinic study

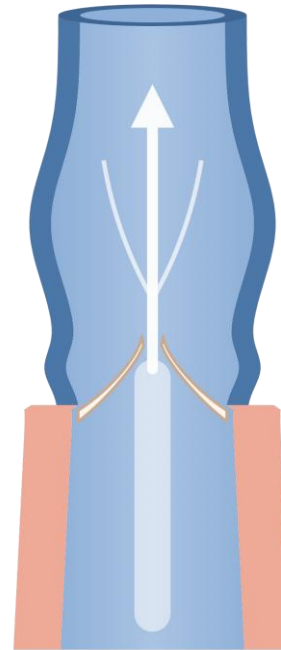


The pulmonary valve (ringed) is the exit from the right side of the heart to the lungs



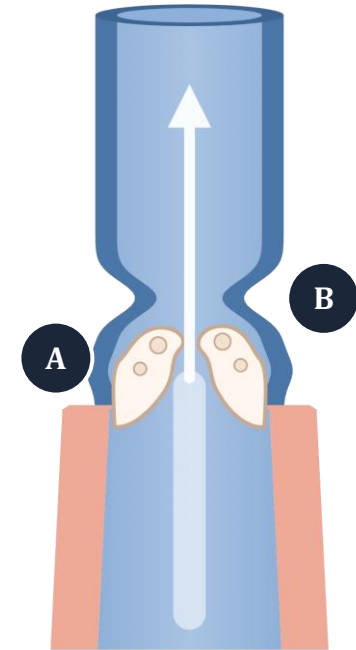
Typical valve

Thin leaflets open wide



Narrowed valve

Thin leaflets stuck together at the edges



Often in Noonan syndrome

Thick leaflets (A); sometimes narrowing above the valve (B)

Watch, stretch or repair

1 · STRUCTURE



Watch

regular scans

Mild narrowing is monitored with regular heart scans

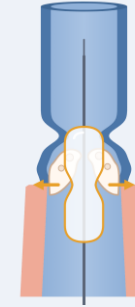
58%

had no procedure during follow-up in a UK study (42 of 73 people; about 12 years)

Stretch

balloon valvuloplasty

A balloon on a thin tube, passed from the groin, is inflated across the valve



1 in 2

needed another procedure when the narrowing extended above the valve

1 in 4

when the narrowing was at the valve only

Birmingham: 54 children; 17 of 32 vs 5 of 22



Repair

heart surgery or intervention

An operation opens the valve, trims thickened tissue and widens the area above it

Often preferred for above-valve narrowing that needs treatment

Italian consensus statement, 2025

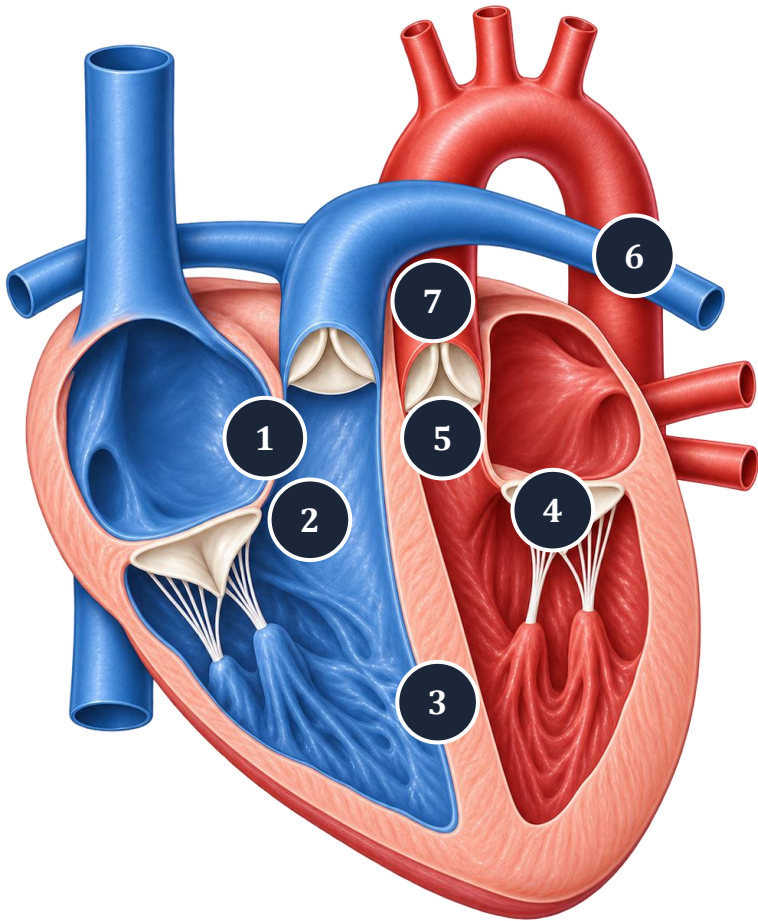


Later, a leaky valve may need replacing by surgery or catheter. Another procedure can be part of the long-term plan.

Look beyond the pulmonary valve

1 · STRUCTURE

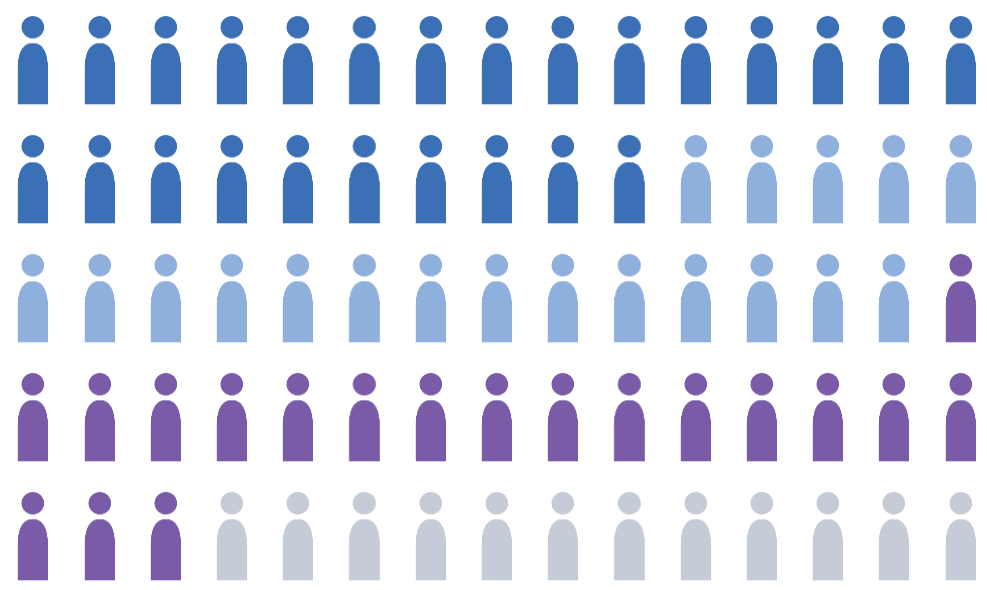
Other differences are common, and their effects can change over time



- 1 Hole between the top chambers (atrial septal defect): **about 1 in 3** in one registry
- 2 Partial atrioventricular septal defect
- 3 Hole between the pumping chambers (ventricular septal defect)
- 4 Mitral valve differences
- 5 Narrowing on the left side, at or below the aortic valve
- 6 Narrow branch pulmonary arteries
- 7 Widened aortic root: about 1 in 5 in a small study; it can increase over time

Our adult clinic in Birmingham

75 adults with Noonan syndrome or a related RASopathy: about 1 in 150 of the patients in our adult congenital heart service



-  Pulmonary valve narrowing only (25)
-  Other or combined pulmonary outflow narrowing (19)
-  Other heart differences, no pulmonary narrowing (19)
-  No structural heart difference recorded (12)

84% have a recorded structural heart difference

Nearly 1 in 3 of those with a heart difference have no pulmonary narrowing at all: we look at the whole heart

Almost 1 in 5 received their syndrome diagnosis as adults

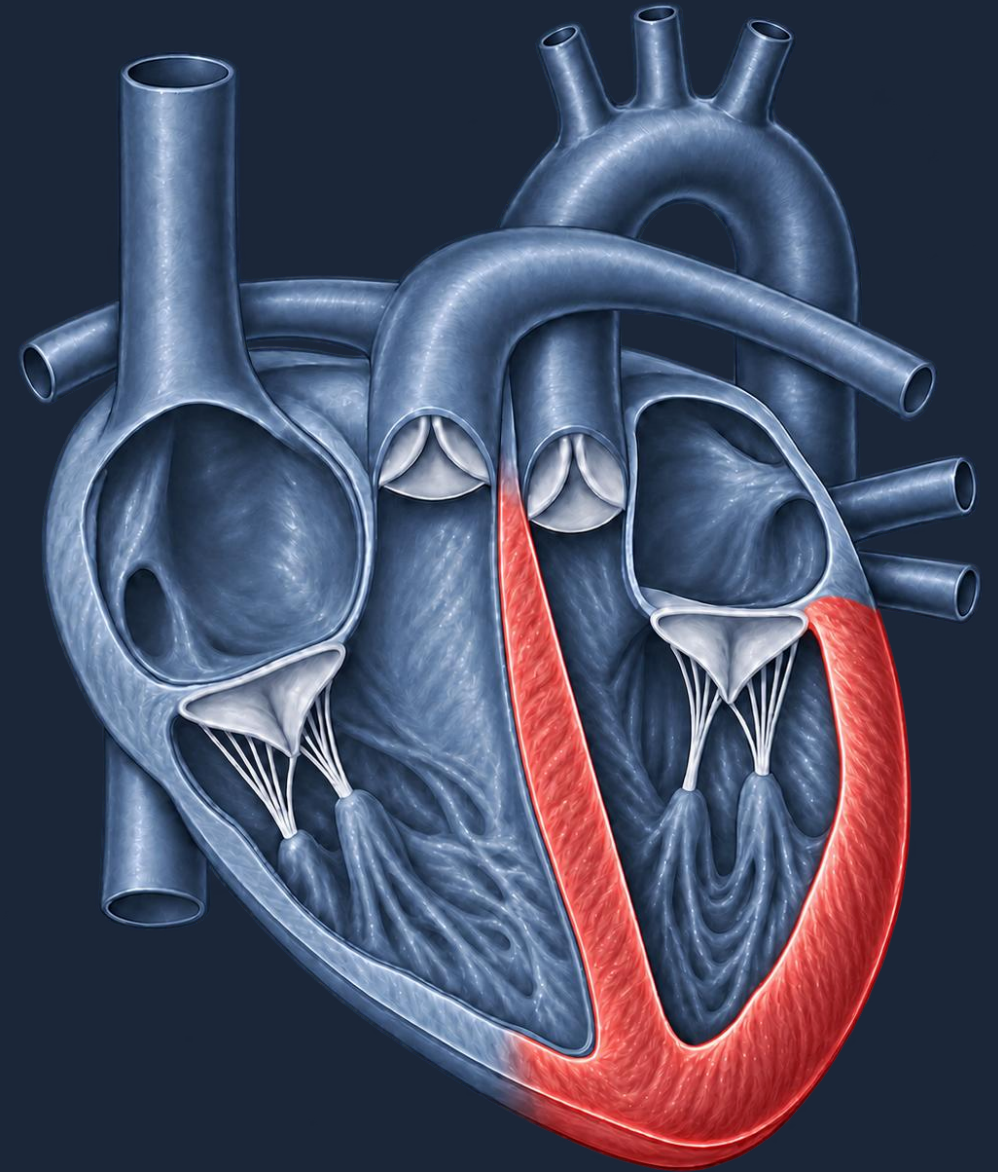
About 1 in 4 have a documented confirmed genetic result. Diagnosed years ago? Ask about modern testing

2

Muscle

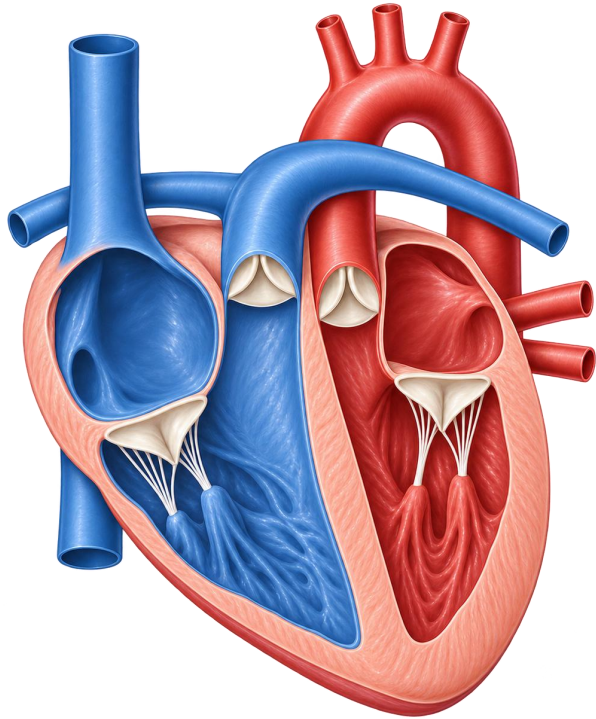
Hypertrophic cardiomyopathy (HCM)

What HCM is · how it changes with age · the role of the gene · treatment

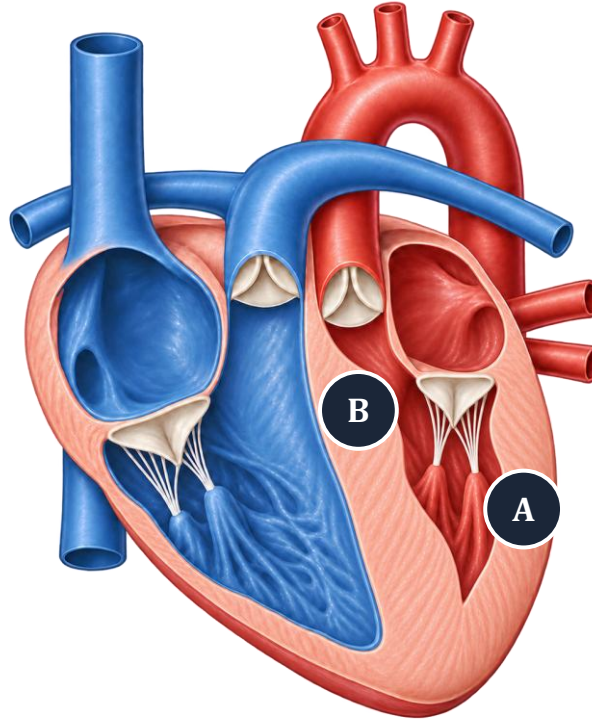


HCM: when the heart muscle is too thick

2 • MUSCLE



Typical heart



Heart with HCM

- A** Thickened muscle can make filling harder
- B** The thickened wall can narrow the exit from the main pumping chamber

About 1 in 5

people with Noonan syndrome have HCM

6 months

by this age, about half were diagnosed in one registry

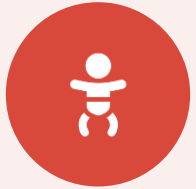
7 in 10

with HCM in one Noonan registry also had a structural heart difference

How HCM can change with age

2 · MUSCLE

Follow-up changes with age; each person's course is different



Babies

Babies with severe HCM need especially close care for heart failure.

We watch: feeding, growth, signs of heart failure



Childhood

Thickness can change. It normalised in about 1 in 6 in one registry.

We watch: wall thickness, the outflow, the ECG



Teenagers

Rhythm problems can occur at any age. Checks remain important as children grow.

We watch: fainting, heart monitor recordings



Adult life

Even if thickening eases, filling and rhythm still need checks.

We watch: filling, atrial size, rhythm



This is why follow-up for HCM continues into adult life, even when the scan looks better

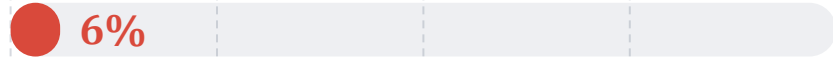
The gene shifts the odds of HCM

2 · MUSCLE

Approximate frequencies in different clinical cohorts

PTPN11

Noonan syndrome



SOS1



All Noonan syndrome

for comparison



RIT1



RAF1



0 25% 50% 75% 100%

NSML: HCM is common

A related condition, usually due to specific PTPN11 variants

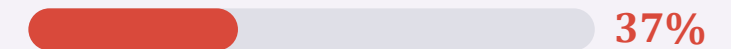
The exact change matters too

RAF1: 203 reported cases

Changes in the CR2 region



Changes elsewhere in RAF1



One change, p.Ser257Leu: 94%

- PTPN11 and SOS1 more often affect the pulmonary valve (about 7 and 6 in 10)
- Recessive LZTR1 can cause significant HCM; timing varies

A gene result guides what we look for. It does not decide what will happen to one person.

Treating HCM: current care and new research

Today



Medicines

Beta-blockers slow the heart and can ease symptoms



Surgery (myectomy)

Removes extra muscle to open the exit



Defibrillator (ICD)

For those at higher risk of dangerous rhythms



Transplant

For selected patients with advanced heart failure

Targeted treatment under study

MEK inhibitors, such as trametinib: medicines first developed for cancer



27 of 31

with usual care



5 of 30

with trametinib added

needed outflow surgery or a transplant, or died

61 children with severe RASopathy HCM; PTPN11 excluded. Not randomised: mainly fewer operations. Side effects: treatment in 33%; dose pause/reduction in 23%.

MEKinRAS: registered randomised trial

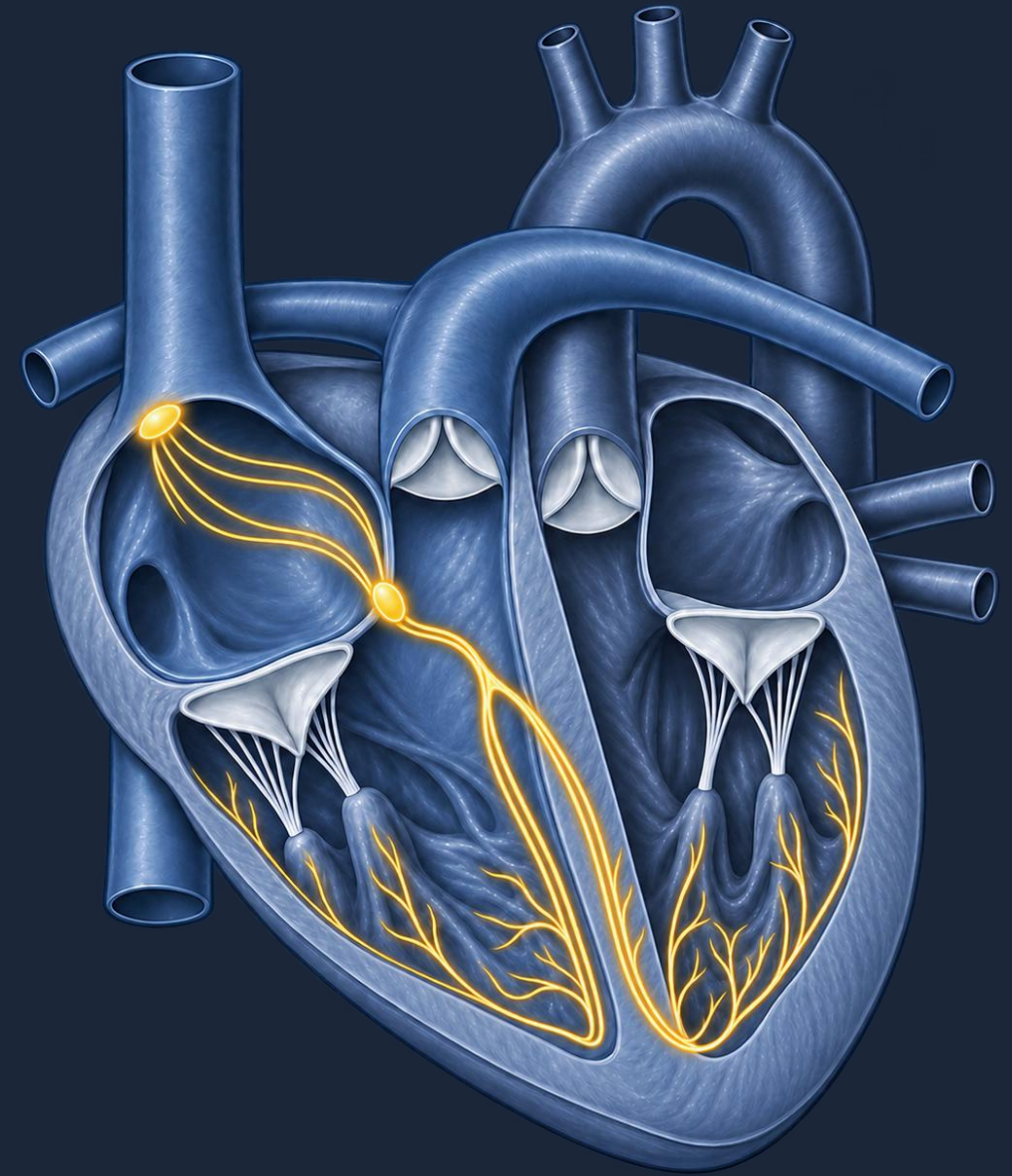
Baby MERIT: for babies, planned for 2027

3

Wiring

Heart rhythm and sudden death

The Noonan ECG · fast rhythms · sudden death in perspective · when to get help



The heart's wiring in Noonan syndrome

1 A different-looking ECG

About 1 in 2 have a characteristic ECG pattern, even with a normal scan. Keep a copy of your usual ECG; your team can explain it.



Some ECG waves look different from usual

2 Fast rhythms in babies / CHD

Atrial tachycardia starts in the top chambers. Common in Costello, also seen in Noonan syndrome (esp. *RAF1*) with or without HCM. It needs treatment and often improves.



Example of a fast atrial rhythm

3 Wiring delays

Reported in about 1 in 4 people with Noonan syndrome with multiple lentigines (NSML). The ECG helps us check for them.



Examples include slower conduction or a wider QRS

Sudden cardiac death is rare in Noonan syndrome

Where there is a risk, it sits mainly with children who have HCM



Noonan syndrome overall

No sudden deaths

in a UK study that followed 112 people, aged 12 to 71, for an average of 12 years. 1 in 5 of them had HCM.



Dangerous heart rhythms are very rare without HCM or another structural heart problem



Children with HCM



95 in 100

have no sudden cardiac event in the 10 years after diagnosis

About 5 in 100 do: much the same as in other childhood HCM

Keeping the risk low



Watch

Regular checks and heart monitors; tell us about any fainting



Protect

A defibrillator (ICD) for those at higher risk



Treat

MEK inhibitors can shrink thickened muscle and may lower this risk; trials are under way

When to get help

3 • WIRING



Call 999

- Collapse or not responding; fainting during exercise or lying down
- Severe breathing difficulty; new blue or grey lips or skin
- Sudden chest pain that persists, or pain with faintness or breathlessness
- Palpitations that persist, or come with chest pain, breathlessness or faintness



Same day: your heart team, GP or NHS 111

- Other unexplained fainting, after full recovery
- New brief palpitations without emergency symptoms
- Increasing breathlessness or unusual tiredness
- Babies: poor feeding, sweating with feeds or fast breathing



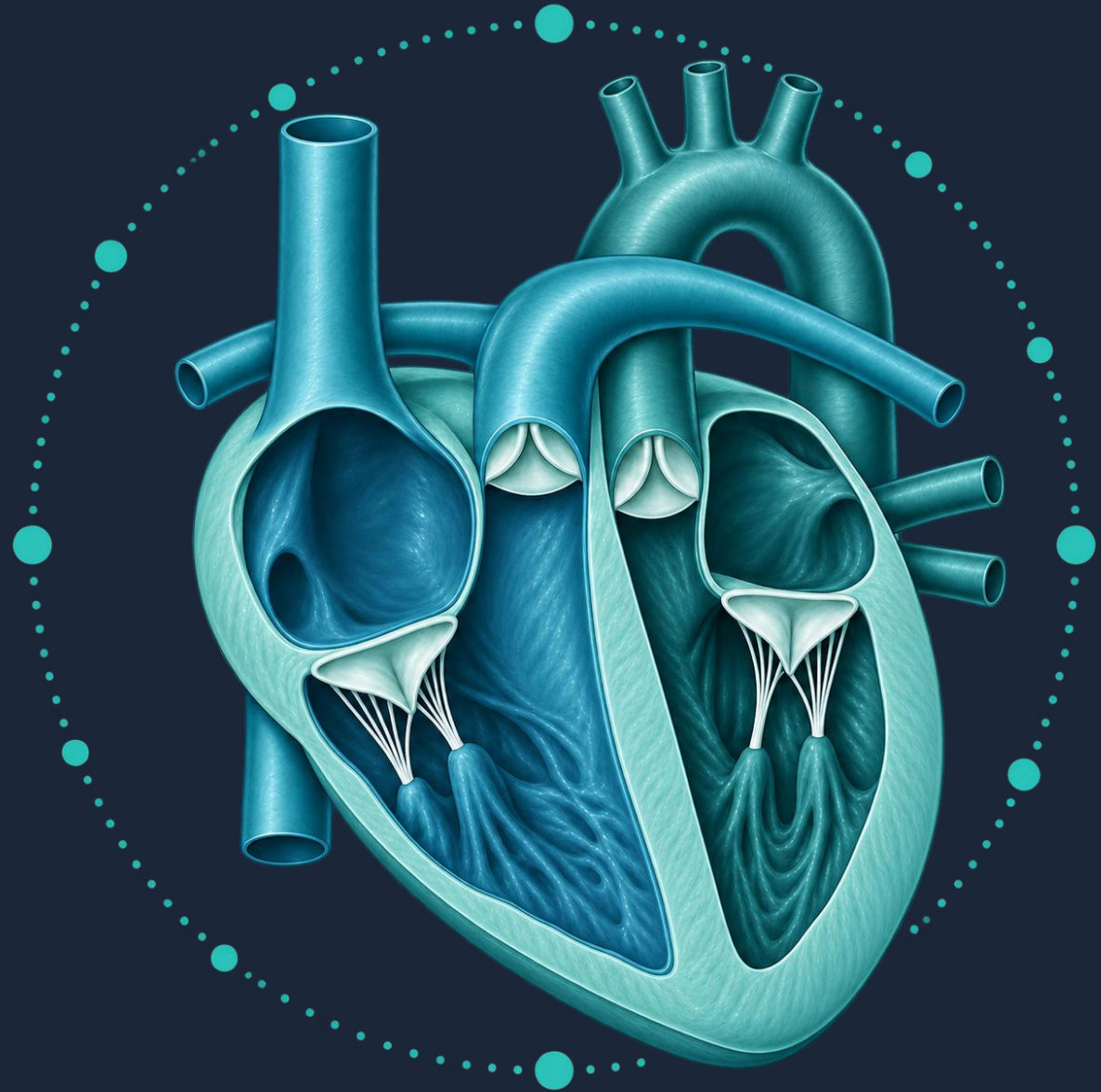
Keep your latest clinic letter and ECG on your phone, and show them at any appointment or A&E visit

4

Check-ups

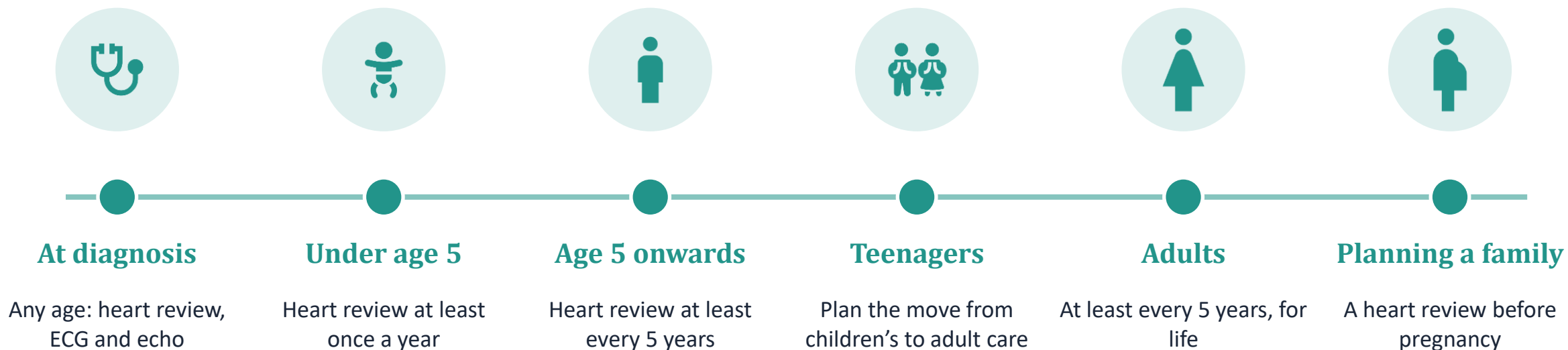
Follow-up when the heart is normal

What guidance advises · your adult care plan · living well



A normal first heart check: what next?

4 · CHECK-UPS



Check sooner if there are

- Symptoms, or changes on the ECG
- A higher-risk genetic finding or NSML
- Plans for growth hormone, surgery or competitive sport

Why keep checking?

HCM may be detected later, valves and the aorta can change, and adult life brings questions such as pregnancy and surgery. Your team sets the scan schedule.

Adult care: a plan that fits your heart

4 · CHECK-UPS

For adults with Noonan syndrome and no known structural heart disease or cardiomyopathy

1



Baseline review

A heart review with ECG and echo. MRI can help if the scan does not give clear enough pictures.

2



A plan for you

If the heart is normal, review at least every 5 years. Your findings, gene result and symptoms guide the plan.

3



Extra tests

A rhythm monitor, exercise test or MRI when needed.

4



Joined-up care

Genetics and possible retesting; planning for pregnancy and procedures; bleeding assessment when needed.

5



Know whom to contact

Ask for a contact plan. New symptoms should not wait for the next routine appointment.



Leave with a clear plan: when is my next review, which tests do I need, and whom do I contact if things change?

Living well: questions families ask

4 · CHECK-UPS



Exercise?

Keep active. With HCM, gentle-to-moderate exercise is usually encouraged. Ask about vigorous or competitive sport.



Growth hormone?

Cardiac safety data are reassuring but limited, especially with HCM. Agree treatment and heart checks with the hormone and heart teams.



Operations?

Tell the team about Noonan syndrome. Arrange a bleeding assessment before procedures, even if routine blood tests were normal.



Teeth?

Brush well and have regular dental checks. Ask whether your heart condition needs antibiotics before invasive dental work.



Pregnancy?

Plan a heart review and genetic advice before pregnancy. With a dominant form, each child has a 1 in 2 chance of inheriting the gene change.



What to carry?

Your clinic letter, usual ECG, medicines and gene result—on your phone or on paper.

Questions research still needs to answer

LOOKING AHEAD

1 Who will develop HCM, and when?

Registries linking the exact gene change to the heart over time

2 Can we predict sudden death in RASopathy HCM?

A tool built for this group; current calculators are not validated

3 Do MEK inhibitors change long-term outcomes?

For whom, at what dose and for how long: trials are under way

4 How should a thick pulmonary valve be treated?

Balloon or surgery first, and when to replace a leaky valve

5 How often should a normal heart be checked?

Best intervals remain uncertain; guidance relies on expert consensus

6 What happens to the heart in adults?

Stiffness, rhythm, the aorta, pregnancy and ageing

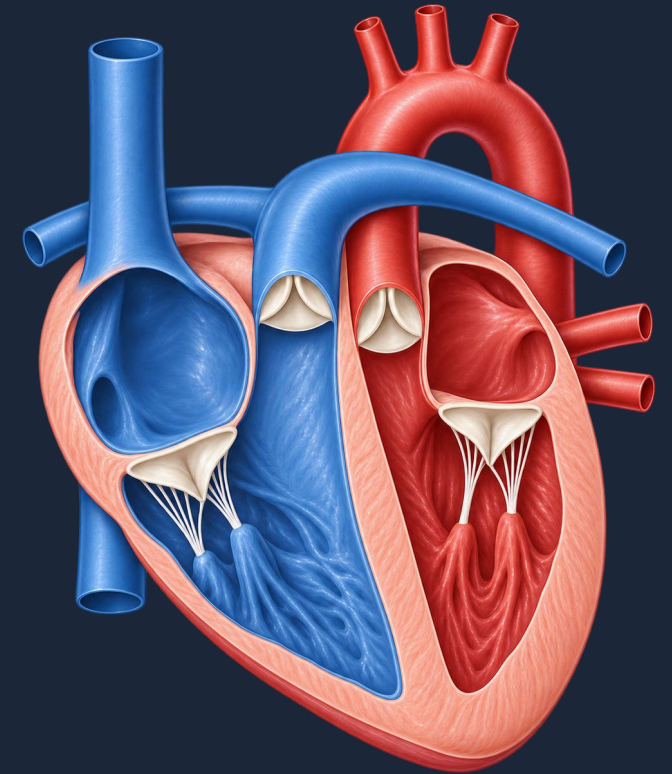


You can help: join registries and studies, and tell researchers which questions matter to you

Five things to take home

- 1 Four parts to know: structure, muscle, wiring and check-ups
- 2 A thick pulmonary valve may need more than one procedure: that is part of the plan
- 3 HCM is often found early. Your gene shifts the odds but does not decide
- 4 Fainting during exercise or lying down: call 999. Other unexplained fainting needs prompt advice.
- 5 A normal scan still means check-ups for life: at least every 5 years for adults

Real hope: treatments targeting the pathway are being tested in clinical trials

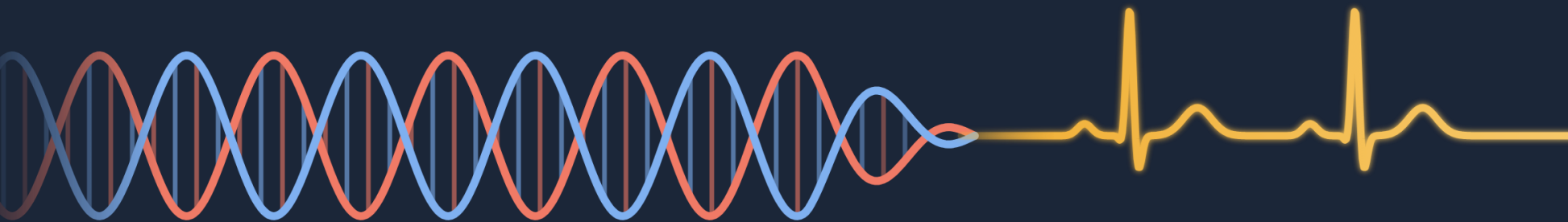
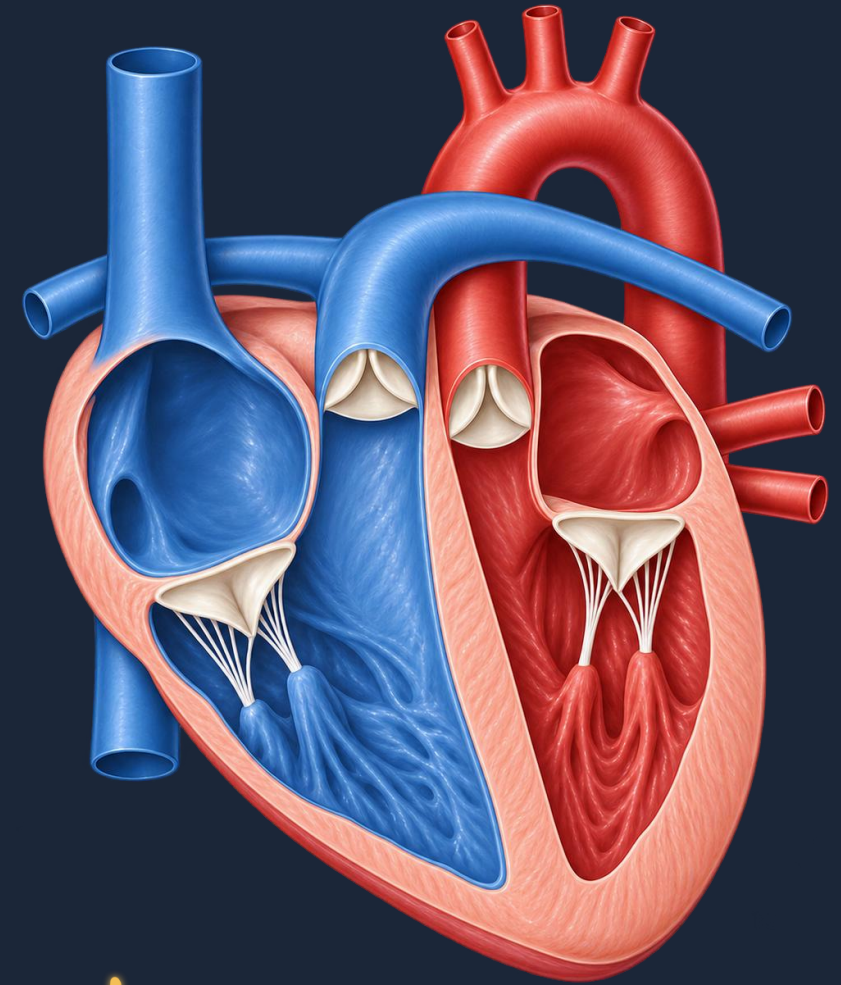


Thank you

Questions welcome

With thanks to the families who share their experiences, the Noonan Syndrome Association, and the adult congenital heart team at Queen Elizabeth Hospital Birmingham

Dr Andrew Constantine · Queen Elizabeth Hospital Birmingham



Gene and heart at a glance

[BACKUP](#)

Gene or condition	Share of Noonan syndrome	Pulmonary stenosis	HCM	Other heart features
PTPN11	about 50%	about 70%	about 6%	Atrial septal defect associated (Boston-based registry)
SOS1	10–13%	about 60%	about 12%	Septal defects about 25%
RAF1	about 5%	not well defined	about 80% (CR2 89%; other 37%)	Often early; severity varies by variant
RIT1	about 5%	common	about 70% in an early series	Septal defects; lymphatic problems
LZTR1	about 8%	variable	reported; notable in the recessive form	Significant HCM can occur; timing varies
NSML (usually PTPN11)	separate condition	about 25%	HCM is common	Conduction defects about 23%
Costello (HRAS)	separate condition	about 10%, usually mild	about 61%	Atrial tachycardia; arrhythmia in 55%

Approximate figures from different, often small referral cohorts; these are not individual predictions. SOS1: 16 patients. RIT1: initial 17-person series.

RASopathy HCM: key outcome studies

[BACKUP](#)

Study	Population	Key findings	Caveats
Lynch, JACC 2023	188 RASopathy HCM vs 567 primary HCM children; 21 centres	Diagnosis: median 0.9 vs 9.8 years. From first review, 10-year SCD 4.7% vs 4.2%; non-arrhythmic death/transplant 11.0% vs 5.4%; ICD insertion 6.9% vs 36.6%	Selected referral cohorts; mixed RASopathies
Boleti, Int J Cardiol 2023	169 children; 15 centres	11 SCD/equivalent events. HCM Risk-Kids C-index 0.60; 6 of 11 events classed low risk. Univariable HRs: syncope 42.2; NSVT 5.5	Few events; wide confidence intervals
Boleti, ESC Heart Fail 2024	149 UK and Irish children; 14 centres	Overall cohort survival: 96% at 1 year, 90% at 5 years, 84% at 10 years. Heart failure, NSVT and outflow gradient: univariable associations with SCD/equivalent	Retrospective; mixed RASopathies; few events
Monda, Circ Genom Precis Med 2023	42 with NSML and HCM	Free of CV death/transplant/appropriate ICD shock: 92.7% at 1 year, 80.9% at 5 years. Serial scans (n=29): absolute regression 31%, progression 21%	Small, selected cohort
Wolf, JACC Basic Transl Sci 2025	61 children with severe RASopathy HCM; 23 centres	Outflow surgery/transplant/death: 5/30 vs 27/31. Death/transplant: 4/30 vs 9/31 (P=0.14). Side-effect treatment 33%; dose pause/reduction 23%	Not randomised; PTPN11 excluded; era effects

Pulmonary valve and structural studies

BACKUP

Study	Population	Key findings
Prendiville, Arch Dis Child 2014	293 with Noonan syndrome (Boston-based registry)	Cardiovascular involvement 81%; PS 57%; ASD 32%; HCM 16%. Reintervention 65% after balloon for valvar PS. HCM regressed in 17%. PTPN11 linked to PS and ASD; RAF1 to HCM
Shaw, Arch Dis Child 2007	112 with Noonan syndrome (UK); mean follow-up 12 years	PS 65% (58% had no intervention during follow-up); HCM 19%; no sudden deaths observed
Abumehdi, Catheter Cardiovasc Interv 2022	54 children with Noonan syndrome having balloon valvuloplasty, 1985–2020	Supravalvar narrowing in 59%. Reintervention 17 of 32 with vs 5 of 22 without (P=0.017); 14 surgical, 8 repeat balloon
Calcagni, Int J Cardiol 2017 (CARNET)	371 with a confirmed RASopathy; 7 European centres	Cardiac involvement 80.3%; estimated 20-year survival 94.3%. HCM under age 2 or in young adults, and biventricular obstruction, linked to cardiac death
Cornwall, Am J Cardiol 2014	37 with Noonan syndrome	Aortic root z-score above 2 in 8/37 (21.6%); measurements increased in a small repeat-imaging group (n=13)
UHB service evaluation 2026 (unpublished)	75 adults in our ACHD service	84% had recorded structural CHD; PS in 65% of these; 30% without pulmonary outflow narrowing; adult syndrome diagnosis recorded in 19%

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36. Heart illustrations created with OpenAI image generation; other illustrations prepared for this talk. Icons: Health Icons (MIT), Material Symbols (Apache 2.0).

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Sources and study qualifications are also included in the relevant speaker notes.