POMPE DISEASE ARE WE MISSING IT OR DIAGNOSING IT TOO LATE?

KENNY GOVENDRAGELOO
PAEDIATRIC CARDIOLOGIST
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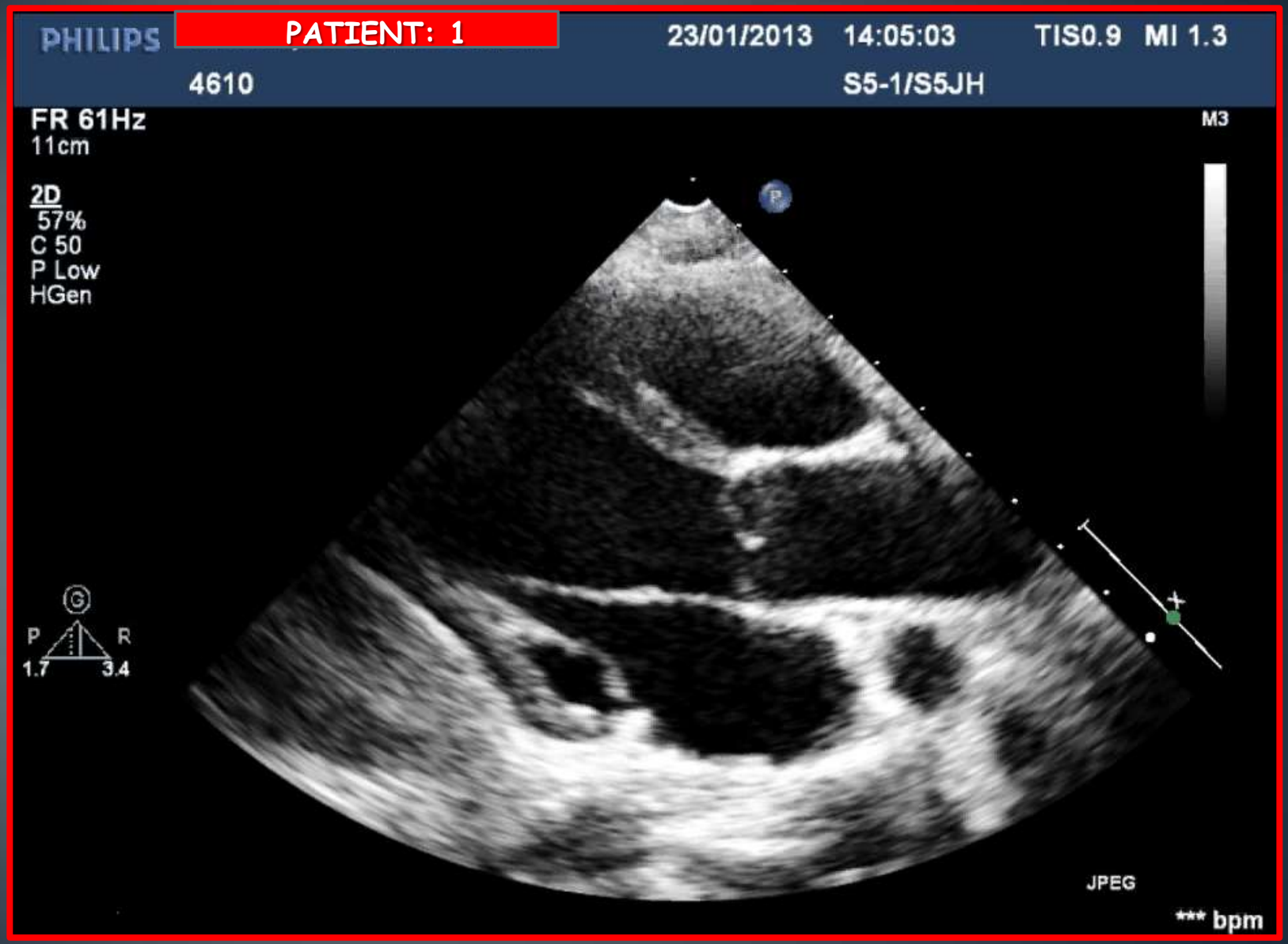
JOHANNESBURG

LYSOSOMAL STORGE DISEASE MEDICAL ADVISORY BOARD MEETING SPONSORED BY GENZYME

POMPE DISEASE
PATIENT 1

- Male infant seen at 17/12 age (03.10.02) – transferred from Duke University Pompe on ERT (trial patient)
- P1: 8 year male
- P2: miscarriage 6/52
- P3: miscarriage 6/52
- P4: 5 year old female
- P5: male died at 6/52 age
- P6: miscarriage 9/52
- P7: male (AEV) born 11.04.01
  - Early evaluation in Durban: hypotonic and enlarged heart -> GOS London confirmed diagnosis -> IT search: trial in Dukes University -> USA/Dukes University: assessed and good candidate -> enrolled into the trial.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C 50
P Low
HGen
M3
P
R
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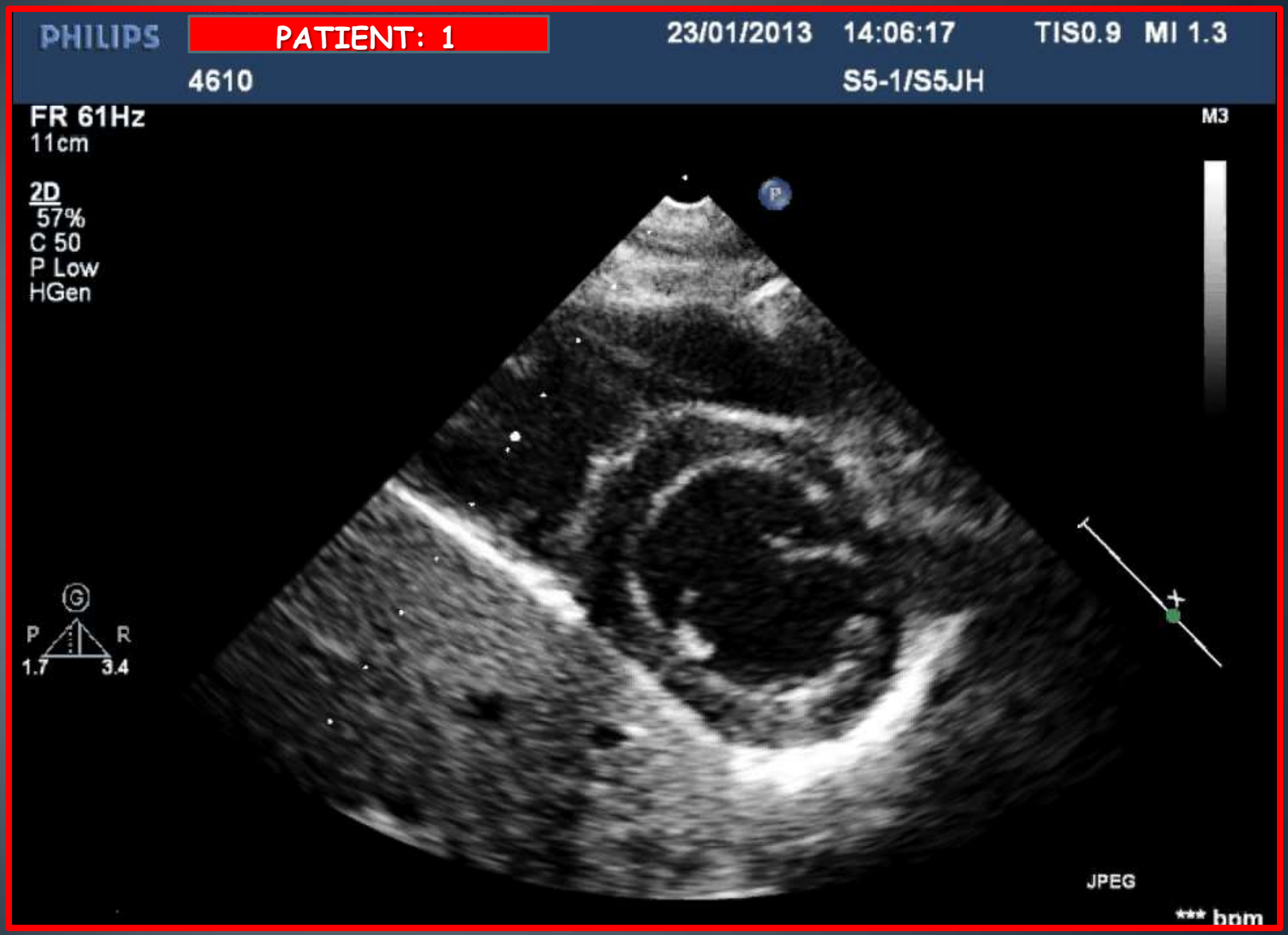
3.4
JPEG
*** bpm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C 50
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P
R
1.7
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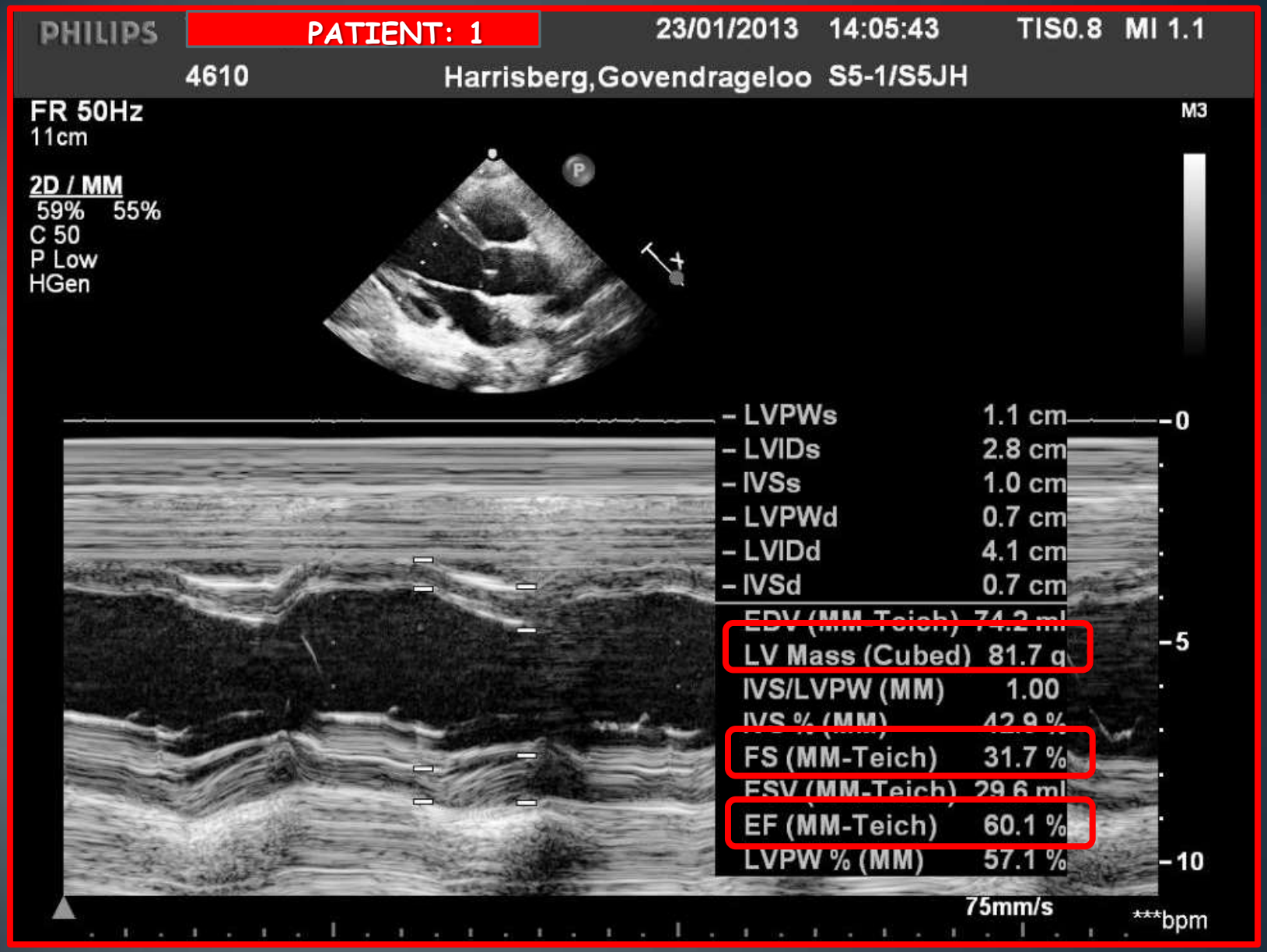
*** bpm



Height: Mean: 101.36g. Range: 75.5 – 142.1g

LVMI: 395.7g/$m^{2.7}$

PATIENT: 1

POMPE DISEASE
PATIENT 2

- Male infant ($14\frac{1}{2}$/12) born 21.11.12 (2^{nd} child); elective C/S 3.8kg
- Older child from a different father
- From 2/12 age: chronic cough + progressive muscle weakness -> admissions for LRTI.
- Admitted for respiratory distress – diagnosed with CCF: paediatric cardiologist
- Admitted to the Sunninghill hospital for evaluation: assisted with investigating for Pompe disease (results obtained about 10/7 later)
- 24.04.13 (5/12 old): took over management

From: To:*00112343148 25/04/2013 11:06 #074 P.001/001

NATIONAL HEALTH LABORATORY SERVICE
University of the Witwatersrand, School of Pathology
Division of Human Genetics

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Page 1 of 1

Labno CGC1302692 (19/04/2013) Patient [redacted]

Ref 4112-40527

DR IN CHARGE
LANCET LABORATORIES
LANCET CORNER
CNR METON & STANLEY ROAD
RICHMOND
2092

FAX->011,358,0839

Address PO BOX 1794
RANDBURG
2125

Age(Sex)DoB 5m (M) 21/11/2012

Ref Dr DR IN CHARGE
Clinic LANCET LABORATORIES - JHB
Patient # 1002996790
Taken 18/04/13 (*) Regd 19/04/13 10:31
(*)=Collection time not stated
Report 25/04/13 11:13

LABORATORY REPORT

Clinical data Genetic testing
POMPE
Specimen Blood
Tests ordered POMPE,Comment

ACID-a-1, 4-GLUCOSIDASE		Flags	Ref Ranges
Patient Activity	1.86 Units		-See below-
Control sent	11.96 Units		

Reference Ranges for Patient Activity
Normal mean (± 1 SD): 13.64 ±2.84 Units
(1 Unit = n moles/hr/mg protein)

The patient appears to have a a severe deficiency of leucocyte acid-alpha-1, 4-glucosidase. This finding is consistent with a diagnosis of Glycogenosis Type II (Pompe disease).

Authorised by : IJ Sinclair Medical Scientist Test(s): POMPE, Comment

for Director

--- End of Laboratory Report ---

PATIENT ACTIVITY: 1.86 Units
CONTROL: 11.96 Units

SCREENING TEST

PATIENT: 2

metabolic laboratory
Hamburg University Medical Center
Department of Pediatrics and Institute of
Clinical Chemistry - Building N23
House N23, Martinistr. 52, 20246 Hamburg
Tel.: +49-40-7410 55026
Fax: +49-40-7410 55984

Universitätsklinikum Hamburg-Eppendorf

Sunninghill Hospital
Dr. G. Sinyangwe

Johannesburg
South Africa

[redacted]
Born: 21.11.2012 (M)
Lab number: 29556370
Sample taken: 04.04.2013,
Received: 12.04.2013, 14:58
Reporting date: 17.04.2013, 16:33
External requestnumber: 121121

Final report

Submitter code: s7977

Dear colleague,

the analysis of the sample which has been sent to our laboratory yielded the following results:

Parameter	Result	Reference range	
Diagnostics of Pompe Disease from Dried Blood			
alpha-glucosidase at pH 3.8	0.25	- 1.5 - 10	nmol/spot*2/h
alpha-glucosidase at pH 7.0	2.69	1.8 - 17.1	nmol/spot*2/h
alpha-glucosidase with inhibition	0	- 0.9 - 7.2	nmol/spot*2/h

Evaluation
Dear colleague,
the activities of alpha-glucosidase at pH 3.8, with and without specific inhibition, are below their respective reference ranges. This is in agreement with classical Pompe disease. We recommend to verify the diagnosis in another dried blood specimen (if possible also in lymphocytes/fibroblasts). In addition, especially if enzyme replacement therapy is under consideration, a molecular genetic work-up should be carried out.
If you have any questions feel free to contact us anytime.

Dr. rer. nat. Z. Lukacs — Prof. Dr. med. R. Santer

α-glucosidase pH 3.8 0.25 -1.5 - 10
α-glucosidase pH 7.0 2.69 1.8 - 17.1
α-glucosidase with inhibition 0.25 -0.9 - 7.2

SCREENING TEST

CENTOGENE
THE RARE DISEASE COMPANY

Centogene AG
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Tel.: +49 (0)381 203652 0
Fax: +49 (0)381 203652 15
Mail: office@centogene.com
Web: www.centogene.com

Centogene AG, Place of Business Rostock • Schillingallee 68 • 18057 Rostock

To Dr. Greenwood Sinyangwe
Sunninghill Hospital
Cnr Nanyuki & Witkoppen Roads, Sunninghill Park

2157 Sandton, Gauteng, Johannesburg
South Africa

Final Report Date: 13.05.2013 Page: 1 of 2

Patient surname, first name: **Mahono, Kubobonke**	Patient date of birth: **21.11.2012**	Sex: **male**
Patient No: **P30340**	Sample received: **06.05.2013**	
Request No: **A136063**	Sample type: **dried blood spot**	5

Request for Pompe disease testing (inheritance: autosomal recessive)

Clinical information: DBS enzyme assay positive for Pompe disease. Request for sequencing only.

Results:
Gene sequencing **GAA** - three heterozygous mutations (c.1124G>T p.R375L, c.2105G>A p.R702H and c.2560C>T p.R854X)

Evaluation:
Three heterozygous mutations in the GAA gene were detected. The first is located in exon 7 (c.1124G>T p.R375L), the second in exon 15 (c.2105G>A p.R702H) and the third in exon 18 (c.2560C>T p.R854X). All mutations have previously been described as disease causing by Pitts, 2008, Qiu, 2007 and Hermans, 1993 (HGMD Professional 2013.1 - PMID: 18429042, 18211760 and 8094615). We further detected a previously unreported heterozygous variant in exon 15 (c.2100C>A p.T700T); it is a synonymous substitution, which does not alter the protein sequence and is therefore likely to be neutral. **We conclude that the patient is suffering from Pompe disease due to mutations in the GAA gene.**

Parental carrier testing is needed to confirm the mutation phase (cis or trans).

Genetic counselling is recommended for your patient and other relevant family members, to explain the results and address any concerns. We also recommend testing a second independent sample from the patient in order to confirm the results (CMGS best practice guidelines).

To confirm this mutation, we will analyse a second independent aliquot. We will contact you again only in case of inconsistent results.

Best regards,

Prof. Arndt Rolfs, MD
Medical Director

Sabrina Bichler, Ph.D
Head of DIT-screening section

Please note: Scientific use of these results requires permission by the investigators. If you would like to download your reports from our web portal, please contact us to receive your login and password. More information is available at www.centogene.com or support@centogene.com.

CLIA registration number: 99D2049715

CAP ACCREDITED

ZLG-P-322.06.13

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Final Report Date: 13.05.2013 Page: 2 of 2

Patient: **Mahono, Kubobonke** DOB: **21.11.2012** Patient No: **P30340** Request No: **A136063**

Additional information
This test was developed and its performance validated by Centogene AG. The US Food and Drug Administration (FDA) has determined that clearance or approval of this method is not necessary and thus neither have been obtained. This test has been developed for clinical purposes. All test results are reviewed, interpreted and reported by our scientific and medical experts. Deviations from the reference sequence at possible polymorphic sites are reported ("SNP site"). Variations from the ancestral allele as reported in the NCBI dbSNP are to be considered clinically irrelevant.

Methods: the GAA gene was analysed by PCR and sequencing of both DNA strands of the entire coding region and the highly conserved exon-intron splice junctions. In addition, a specific PCR to screen for the common deletion of exon 18 was also performed. The reference sequence of the GAA gene is: NM_000152.3.

GAA (Glycogen storage disease II - GSD II, OMIM 232300)
Inheritance: autosomal recessive
Reference sequence: NM_000152.3

Location	Nuc. Change	AA change	Ref.	Evaluation
Ex02	c.324T>C (homo)	p.C108C	rs1800300	SNP site
Int02	c.547-4C>G (homo)		rs3816256	SNP site
Ex03	c.596A>G (homo)	p.H199R	rs1042393	SNP site
Ex03	c.668G>A (homo)	p.R223H	rs1042393	SNP site
Int04	c.858+8ins7bp (homo)	-	rs35373675	SNP site
Ex05	c.921A>T (het)	p.A307A	rs1800303	SNP site
Int05	c.955+12G>A (homo)	-	rs2252455	SNP site
Ex07	**c.1124G>T (het)**	**p.R375L**	**Pitts, 2008**	disease-causing
Ex08	c.1203G>A (homo)	p.Q401Q	rs1800304	SNP site
Int08	c.1327-18A>G (homo)	-	rs2278619	SNP site
Ex09	c.1374C>T (het)	p.Y458Y	rs1800305	SNP site
Int09	c.1438-19G>C (homo)	-	rs2304844	SNP site
Ex15	c.2100C>A (het)	p.T700T	none	likely neutral
Ex15	**c.2105G>A (het)**	**p.R702H**	**Qiu, 2007**	disease-causing
Ex17	c.2338G>A (homo)	p.V780I	rs1126690	SNP site
Ex18	c.2553G>A (het)	p.G851G	rs1043397	SNP site
Ex18	**c.2560C>T (het)**	**p.R854X**	**Hermans, 1993**	disease-causing
3' UTR	c.*91G>A (het)	-	rs2229721	SNP site
3' UTR	c.*1580>T (het)	-	none	likely neutral

CAP ACCREDITED

ZLG-P-322.06.13

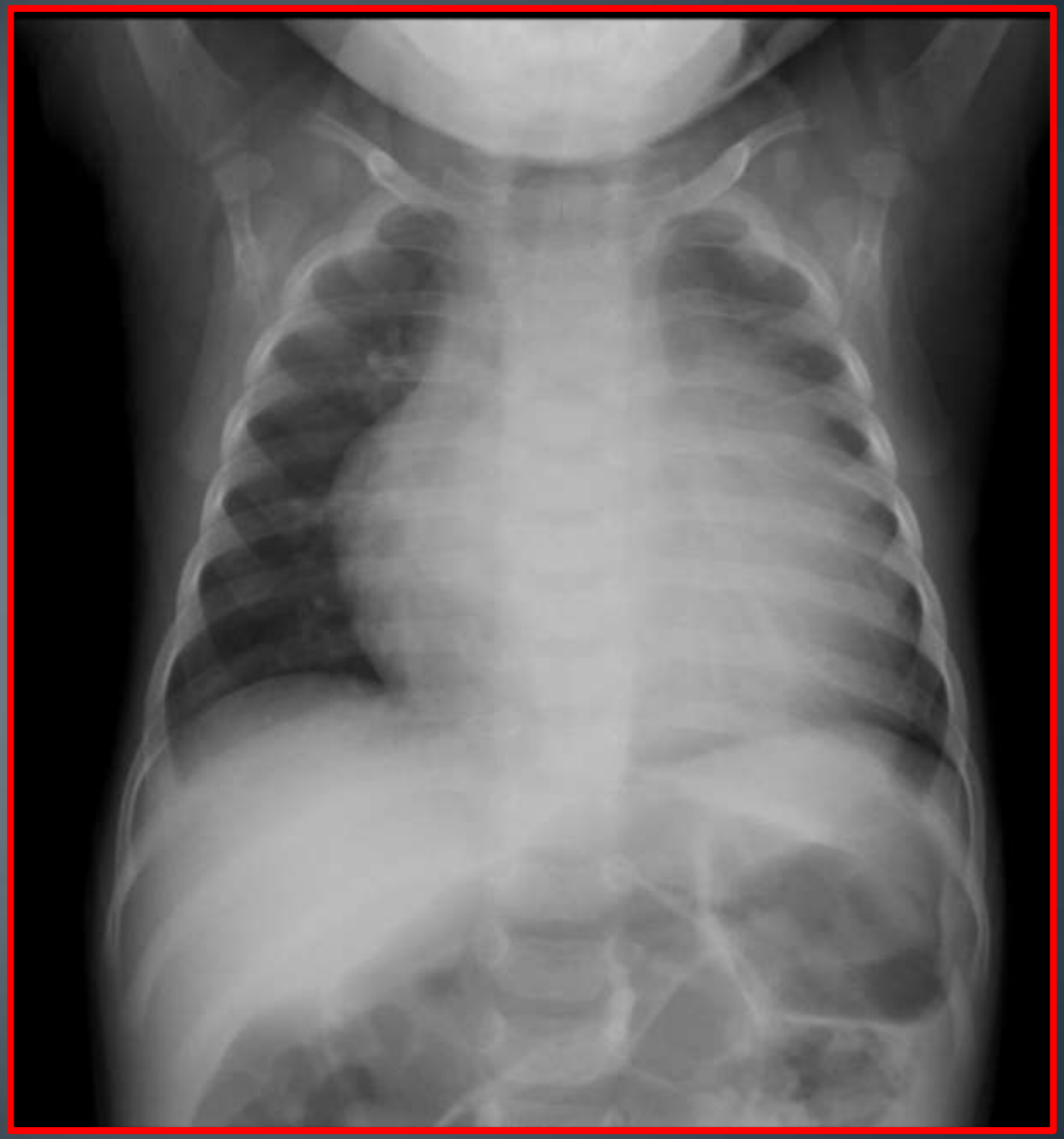
PATIENT 2: CONFIRMATORY TEST GENETICS

PATIENT: 2

PATIENT: 2


PATIENT: 2

PATIENT: 2



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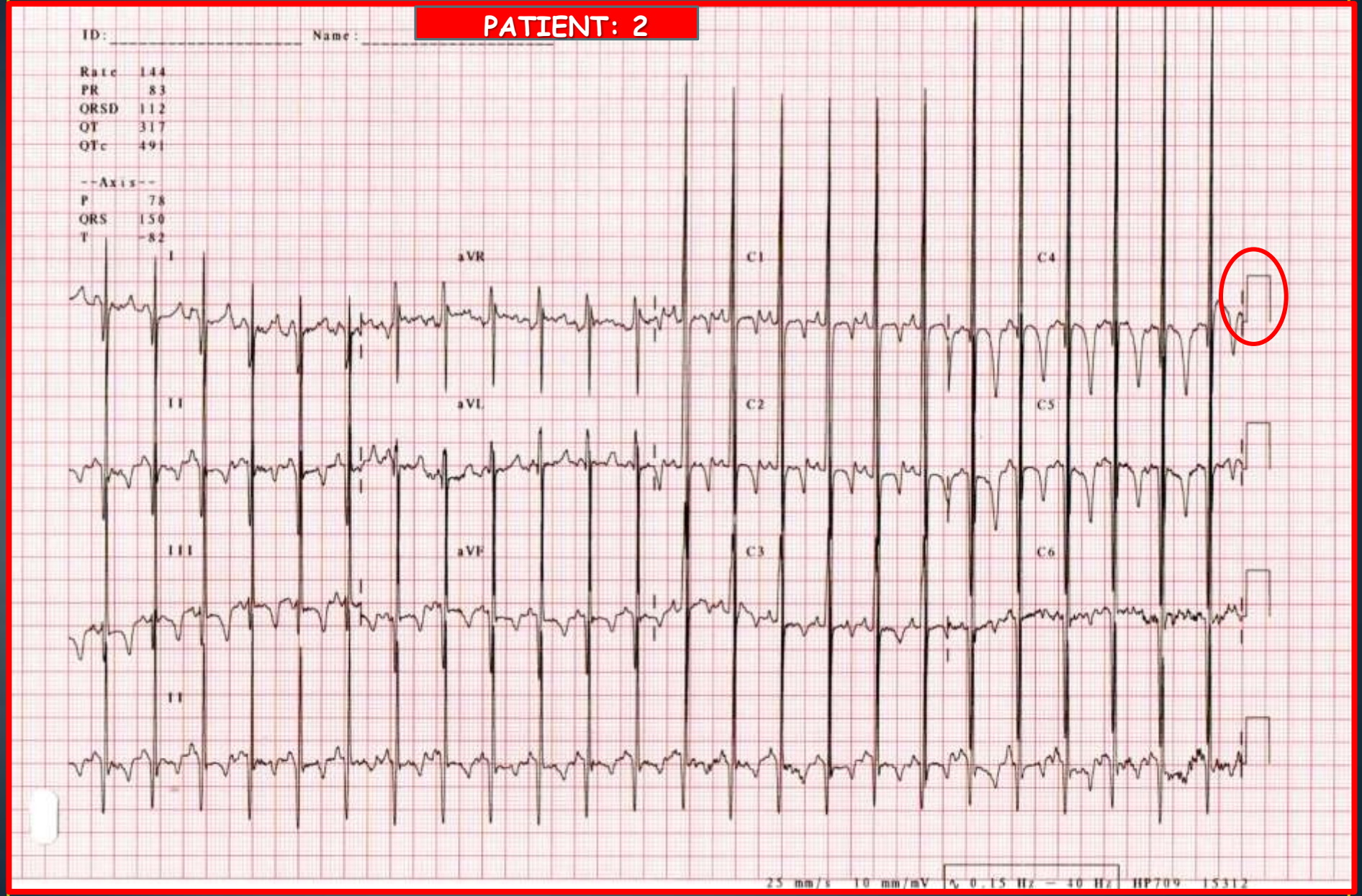
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C4
II
aVL
C2
C5
III
aVF
C3
C6
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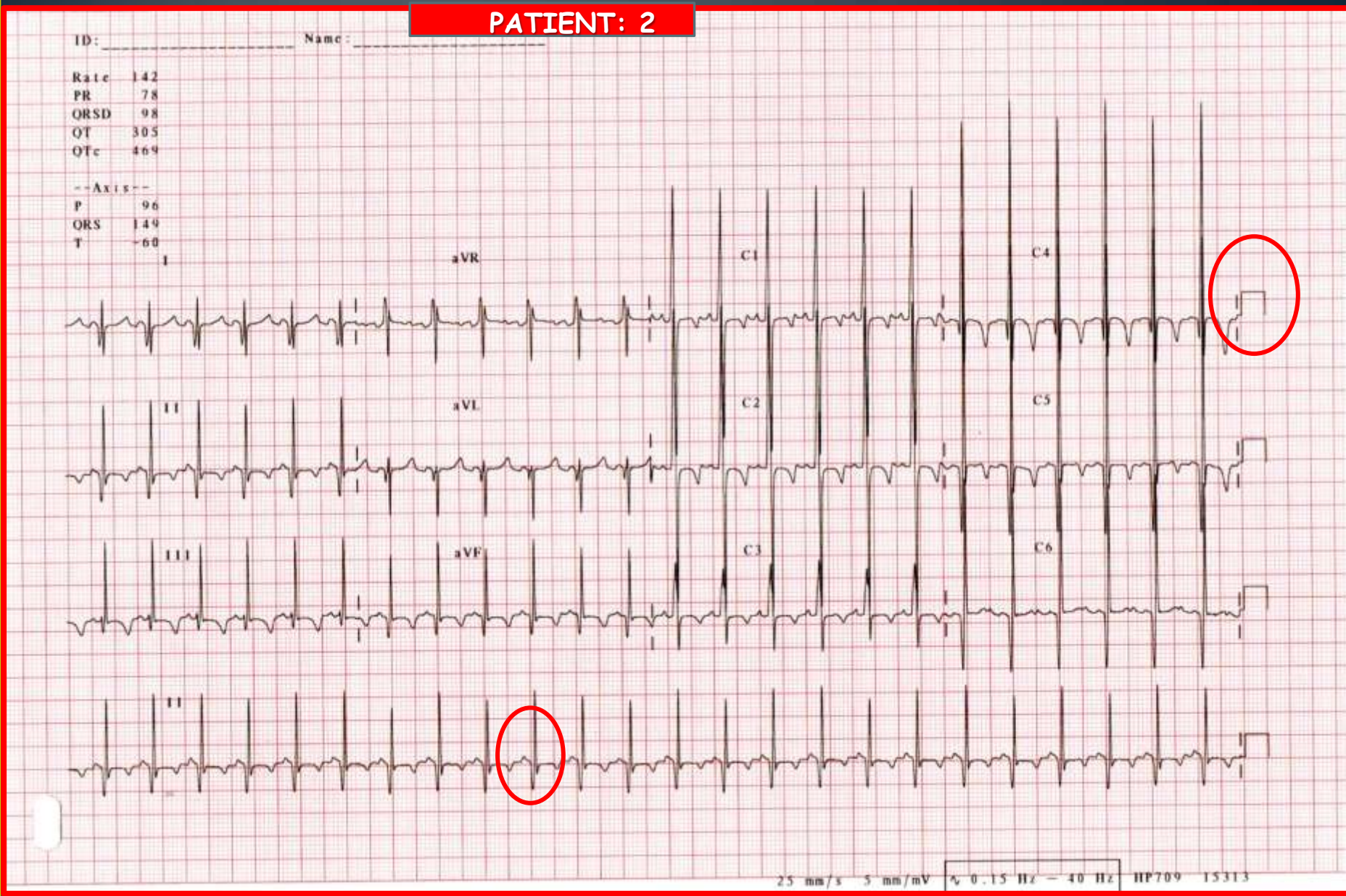
0.15 Hz - 40 Hz
HP709 15312

PATIENT: 2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C4
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C5
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C3
C6
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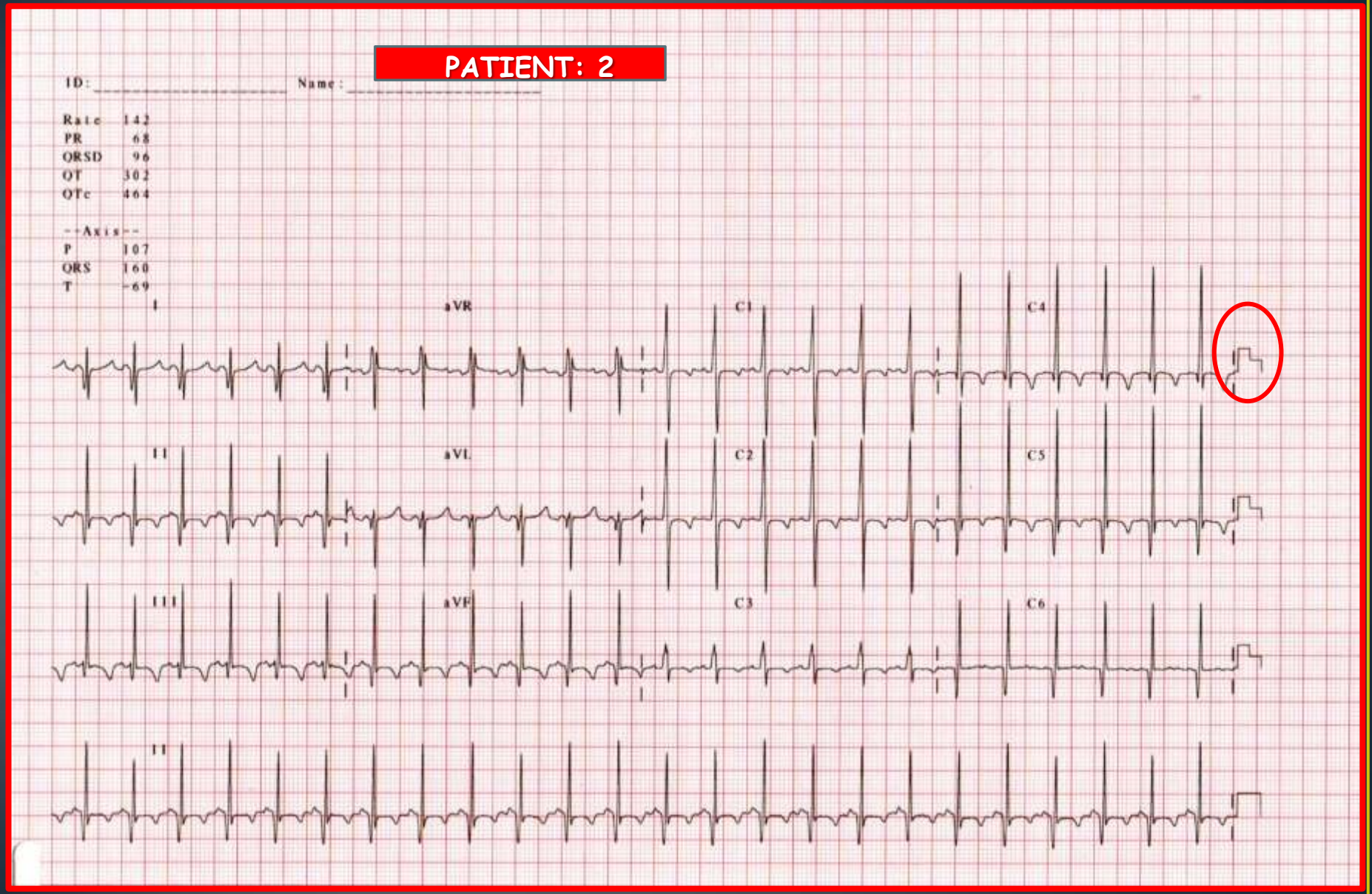
25 mm/s 5 mm/mV 0.15 Hz - 40 Hz HP709 15313

PATIENT: 2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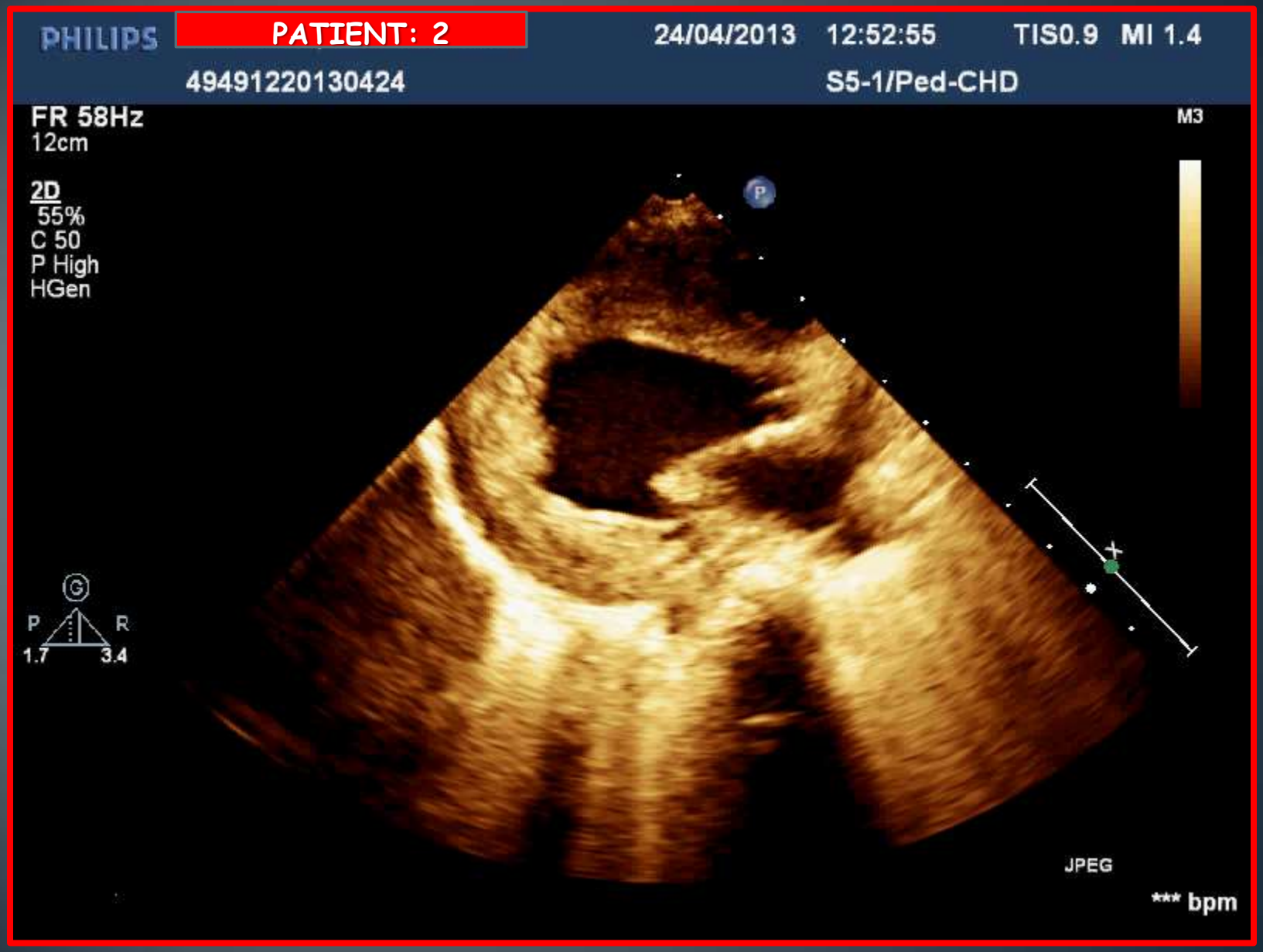
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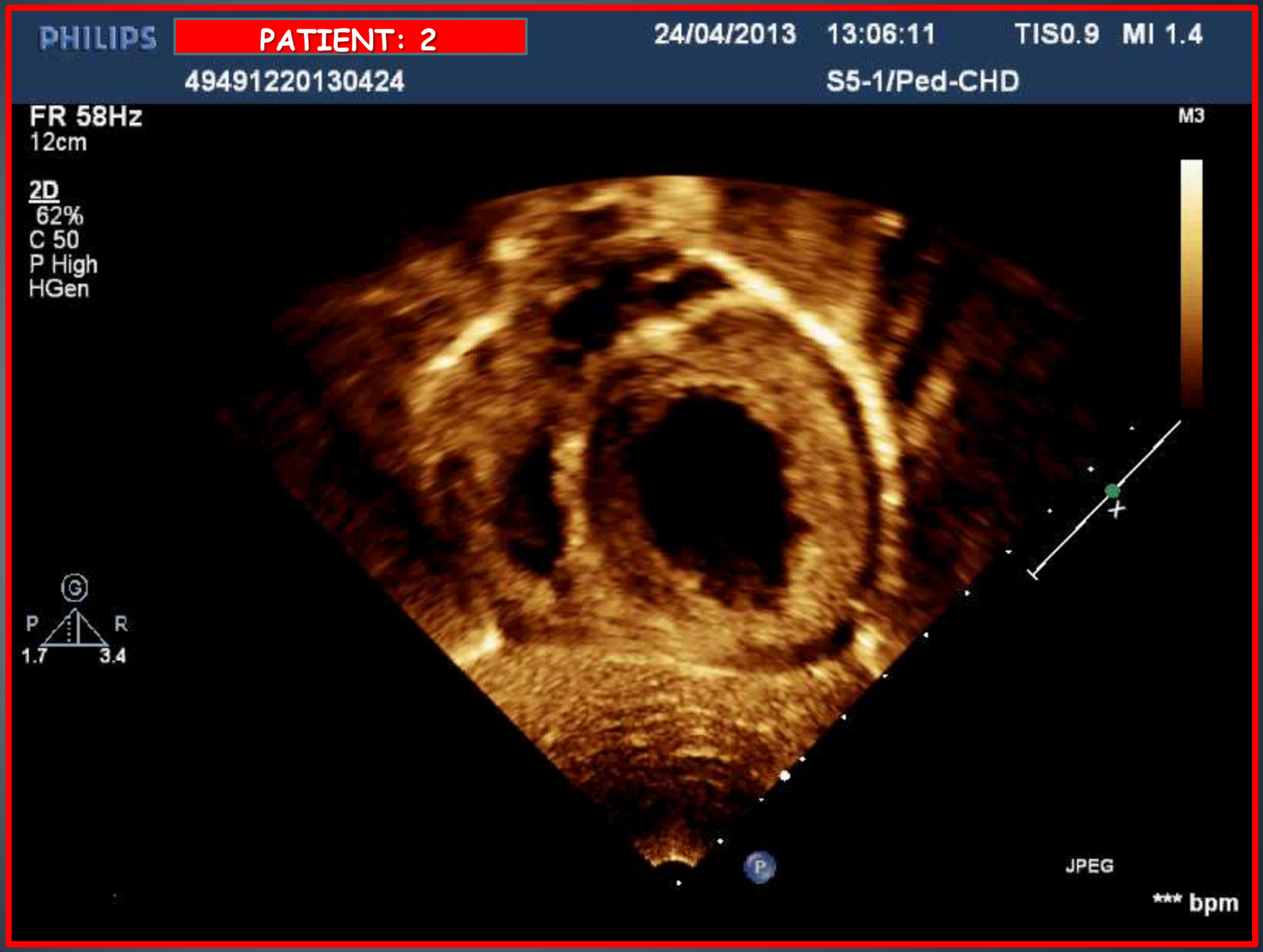
C 50
P High
HGen
M3
G
P
R
1.7
3.4
JPEG
*** bpm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62%
C 50
P High
HGen
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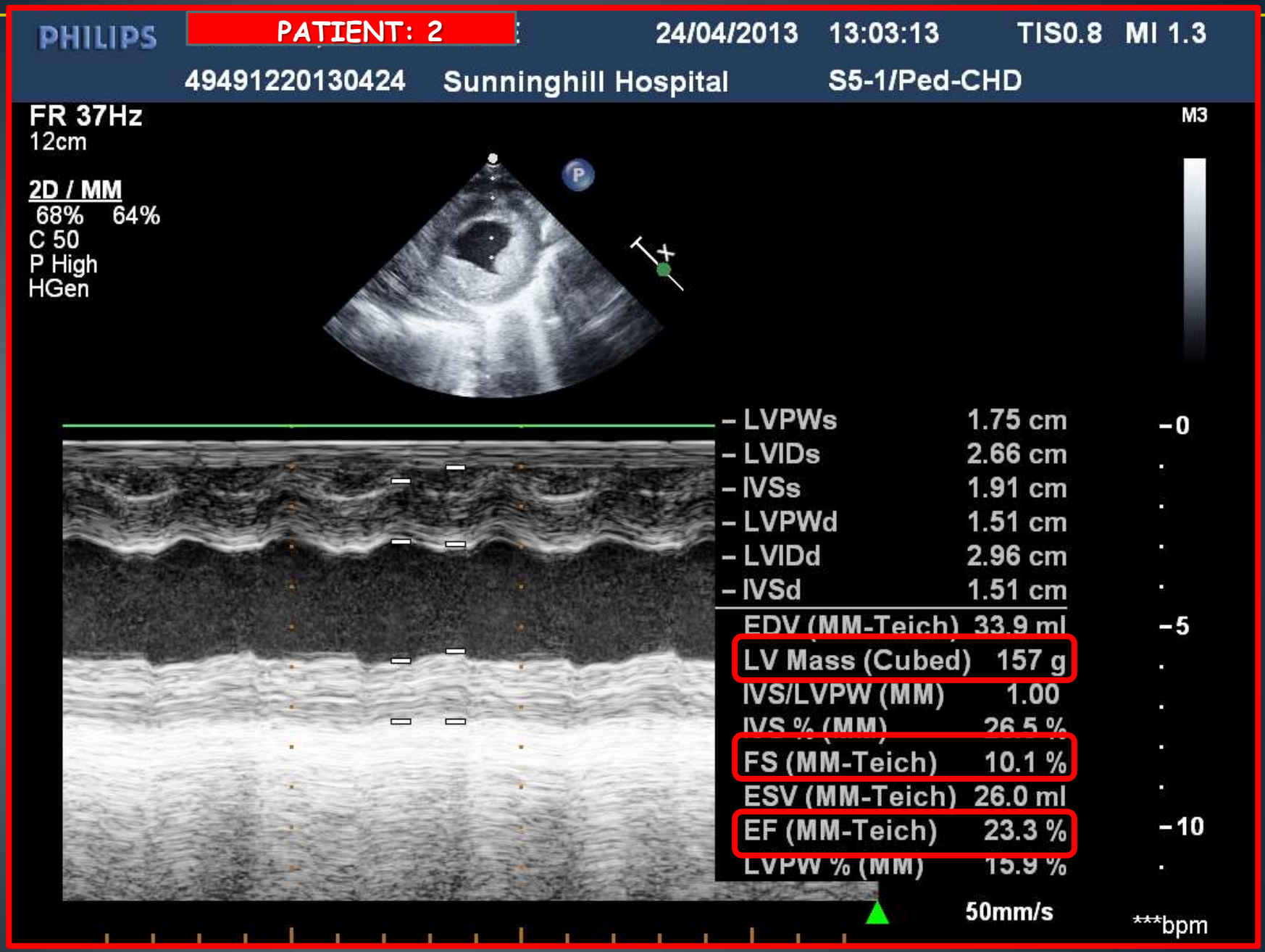
1.7
3.4
JPEG
*** bpm



Height (71cm) Mean: 25.5g. Range: 18.65-34.6g

LVMI: 395.7g/$m^{2.7}$

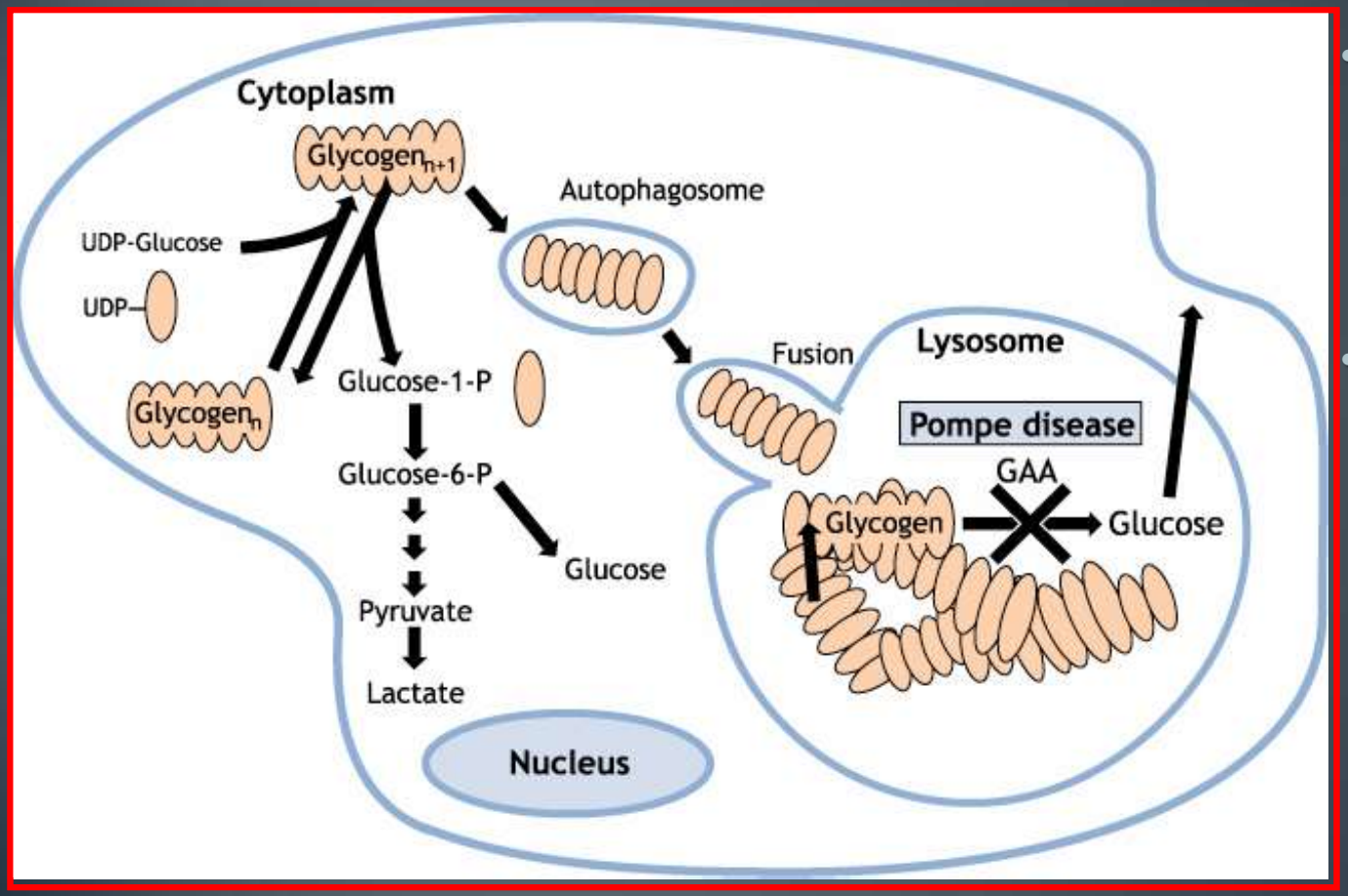
Infusion completed 7 hours ago (01h00)
Video 08h00

PATIENT: 2

POMPE DISEASE: OVERVIEW

- Progressive, multisystemic, debilitating and often fatal neuromuscular disorder
- 1932: Dutch pathologist, Joannes C Pompe. 7/12 child died from idiopathic cardiac hypertrophy – massive glycogen accumulation in many tissues but predominantly in skeletal and cardiac muscles.
- Encompasses a single disease continuum with variable rates of disease progression.

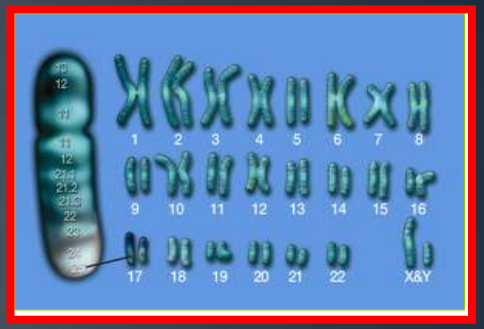
POMPE DISEASE: PATHOGENESIS



- *GAA enzyme essential for degradation of lysosomal glycogen*
- Inherited enzyme deficiency results in glycogen accumulation and lysosomal distention

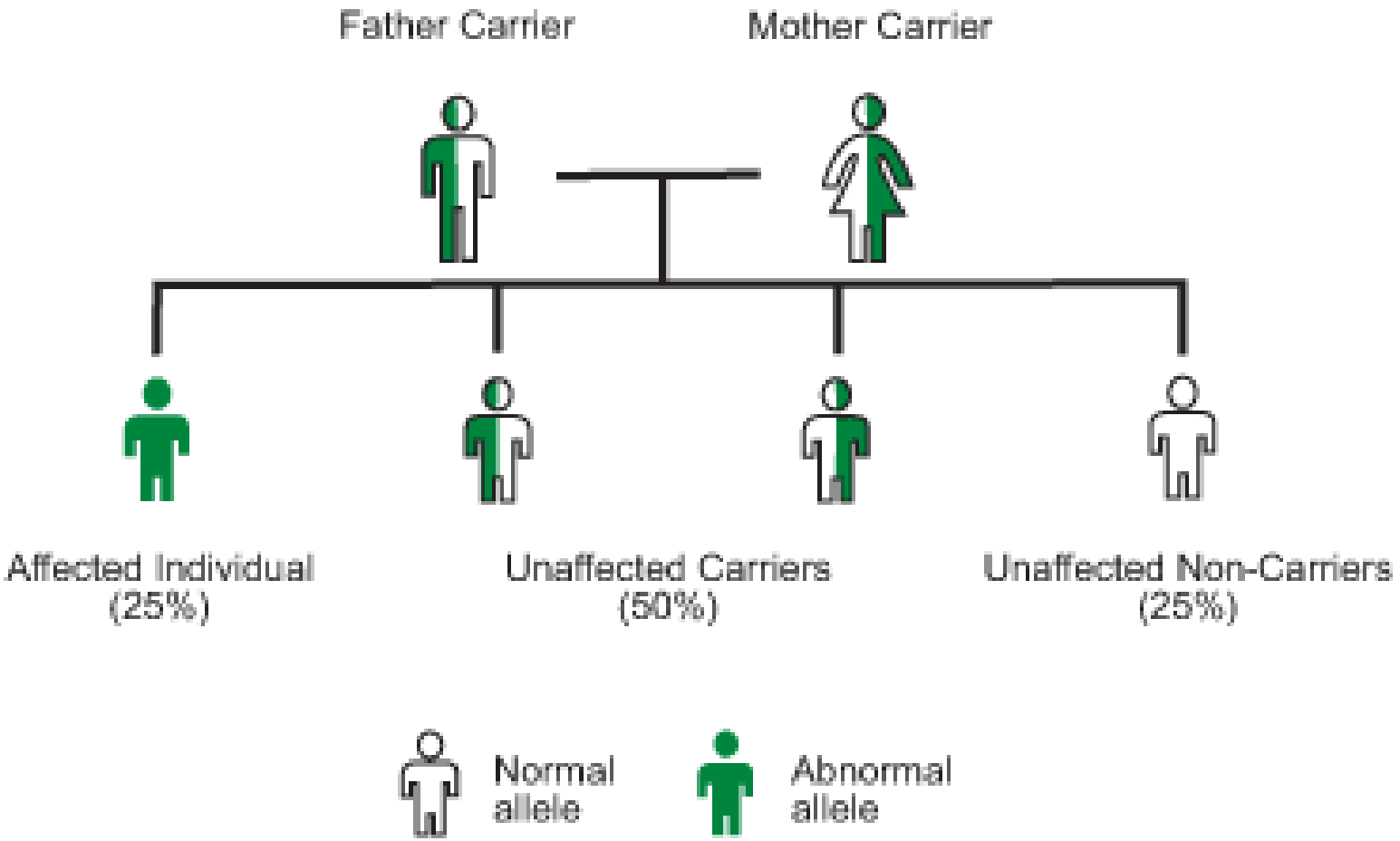
POMPE DISEASE: GENETICS

- Autosomal recessive disorder – affects both sexes equally
  - Copy of mutated *GAA* gene from each parent



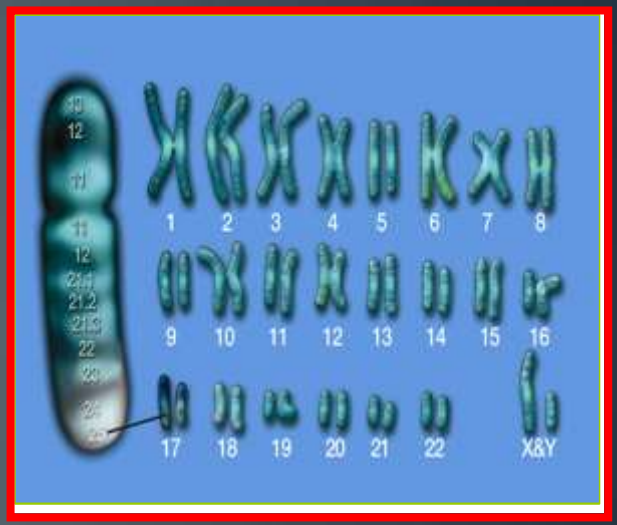
  - Each child born to 2 carriers
    - 25% chance of inheriting Pompe disease (17q25)
    - 50% chance of being a carrier (lower than normal enzymatic activity)
    - 25% chance of being completely unaffected
  - Less common scenarios:
    - One parent has Pompe disease and the other is unaffected: all children will be carriers, but none will develop the disease
    - One parent has the disease and the other is a carrier: each child will have a 50% chance of inheriting the disease and 50% chance of being a carrier

POMPE DISEASE
GENETICS



POMPE DISEASE: GENETICS

- 1979: gene traced to the long arm of chromosome 17 (location: 17q25)



- Status of carriers:
  - Phenotypically normal – one normal *GAA* gene produces sufficient enzyme activity to prevent the excessive lysosomal deposition of glycogen.
  - Compared to unaffected individuals, the carriers display lower than normal enzyme activity

POMPE DISEASE: BACKGROUND

- All GSDII patients have same general disease course with steady intralysosomal accumulation of glycogen in target tissues (skeletal; cardiac and smooth muscle) leading to:
  - Progressive debilitation
  - Organ failure and/or
  - Death
- Severity varies by:
  - Age of onset
  - Organ involvement including degree and severity of muscular involvement (skeletal, respiratory and cardiac) and
  - Rate of progression

POMPE DISEASE: BACKGROUND

- GSDII: single enzyme deficiency -> continuum of disease spectrum varying by
  - Age of onset
  - Organ involvement and
  - Degree of myopathy

- Classify GSDII
  - Infantile form
  - Late-onset form

POMPE DISEASE: BACKGROUND

- INFANTILE FORM:
  - Classic Infantile Pompe Disease - rapidly progressive disease characterised by
    - Prominent cardiomegaly
    - Hepatomegaly
    - Weakness and hypotonia
    - Death due to cardiorespiratory failure in the first year
    - Most severe end of disease spectrum
  - Infantile variant form (non-classic infantile: <1 year)
    - Slower progression
    - Less severe cardiomyopathy

POMPE DISEASE: BACKGROUND

- LATE-ONSET FORM:
  - Childhood; juvenile or muscular variant (heterogeneous group) presenting
    - Later than infancy and
    - Typically not including cardiomyopathy
  - Adult-onset form characterised
    - Slowly progressive myopathy predominantly involving skeletal muscle
      - First presentation as late as 2nd -> 6th decade of life

POMPE DISEASE: BACKGROUND

- Important to recognise that age of onset does not always delineate subtypes well
  - Occasional 'juvenile-onset' or mild variant cases may present prior to 12 months of age
  - Clinical presentation must be considered along with age of onset when classifying cases

- Incidence: 1:14 000 – 1:300 000 (combined 1:40 000)
  - Influenced by ethnicity and geographical area studied
    - Infantile form: higher incidence ~ African-Americans and Chinese
      - 1:183 000 (Netherlands)
    - Late-onset: higher incidence in Netherlands
    - Birth rate in South Africa: 19.14:1000
    - 2011: total number of registered births 1 202 377 (30 cases per annum)

POMPE DISEASE: NATURAL HISTORY

- Clinical presentation of GSDII:
  - Rapidly progressive infantile form which is uniformly lethal
  - Signs and symptoms (Classic Infantile form):
    - Cardiomegaly
    - Cardiomyopathy
    - Hypotonia
    - Muscle weakness
    - Respiratory distress
    - Respiratory infections
    - Feeding difficulties and
    - Failure to thrive

POMPE DISEASE: NATURAL HISTORY

- Clinical presentation of GSDII (Infantile-onset):
  - Median age at symptoms onset: 1.6 months (Dutch:20 & Cohort:133)
  - Median age at diagnosis/death: 5.3/7.7 (Dutch) and 4.5/6.0 (literature cohort)
  - Median age at symptoms onset: 4 months (Worldwide cohort: 168 patients)
  - Median age first ventilator support: 5.9 months
  - Median age of death: 8.7 months

POMPE DISEASE: NATURAL HISTORY

- Late-onset GSDII (present at any age) – characterised:
  - Lack of severe (typically absence of) cardiac involvement and
  - Less dismal short-term prognosis
  - Symptoms ~ progressive skeletal muscle dysfunction
    - Proximal lower limb and paraspinal trunk muscles followed by
    - Diaphragm and accessory muscles of respiration
    - Wheelchair users and assisted ventilation
    - Morbidity and mortality ~ respiratory failure

POMPE DISEASE
CLINICAL EVALUATION: INFANTILE & LATE-ONSET

- CXR: massive cardiomegaly
- ECG: short PR interval and tall QRS complexes
  - Voltage calibration
  - Age adjusted norms for PR interval
  - Late-onset: rarely show cardiomegaly (CXR and ECG)
- ECHO (infantile form):
  - Early stage: HOCM – with/without LVOTO
  - Late stage: DCMO with impaired function

POMPE DISEASE:
IMPORTANCE OF EARLY DIAGNOSIS

- Recognising Pompe disease can be challenging – Signs & Symptoms may be heterogeneous and shared with other disorders
- Early diagnosis is critical to optimise disease management outcomes
- Challenge of recognising Pompe disease may result in delayed diagnosis

POMPE DISEASE
DIAGNOSTIC PATHWAY

- Recognising the physical symptoms of Pompe disease
- Performing specific laboratory tests: SCREENING
- Finally, performing CONFIRMATORY tests

POMPE DISEASE
DIAGNOSTIC PATHWAY

- SCREENING TESTS
  - GAA enzyme assay:
    - Lymphocytes (blood)
    - Conclusive diagnosis: absent or markedly reduced GAA enzyme activity
      - Residual activity can be anywhere from less than 1% (generally in infants) to 40% of normal levels
    - Local at NHLS with control sample
    - Enzyme assay in Hamburg

POMPE DISEASE
DIAGNOSTIC PATHWAY

- CONFIRMATORY TESTS
  - Fibroblasts (skin biopsy)
    - Cell culture: 4-6 weeks ~ delay in diagnosis
  - Muscle biopsy
    - Risk of General Anaesthesia
    - Great care in handling sample
    - Liquid nitrogen and shipped on dry ice
    - Late-onset disease: site of biopsy important
      - Variability of glycogen accumulation between different muscles and between the muscle fibre type within the muscle
  - Genetic studies: CENTOGENE AG

POMPE DISEASE
LABORATORY TESTING

- Clinical diagnosis traditionally confirmed by virtual absence (infantile-onset) or markedly reduced (late-onset) GAA activity in tissues such as
  - Cultured fibroblasts – skin biopsy (GAA activity most reliable). Gold standard test. 4-6 weeks
  - Muscle biopsy (GAA activity most reliable)
  - Blood
    - Purified lymphocytes; mononuclear cells and lymphoid cell lines (done with appropriate inhibitors to inhibit the interfering maltase-glucoamylase – MGA)
    - DBS
  - Urine: elevation of Glc4 – biomarker. Ancillary diagnostic test.
  - Mutation analysis

POMPE DISEASE
LABORATORY TESTING: SOUTH AFRICA

- NHLS: Leucocyte enzyme assay
  - Logistics:
    - Patient's sample in special tube + Volume of blood
    - Control sample
    - Wrapped in tissue and placed on ice-brick in polystyrene container
    - Preferable for sample to reach NHLS at midday – within about 3 hours after sample is drawn
    - Where possible: AVOID TESTING ON A FRIDAY
    - Inform Ian Sinclair about samples he is to receive

POMPE DISEASE
LABORATORY TESTING: SOUTH AFRICA

View LAB Test Dictionary

Print # 5820.060 Mnemonic POMPES DISEASE Name POMPES DISEASE (MALS CENT)

Additional Charges
Pri Charge Test

Timed Test? N
Tmd Result Text
Default Tmd Test
Auto Recv Prim Spec?

Inf Ctrl Screen

Timed Labels Test | Min Col Cat
1
2
3
4

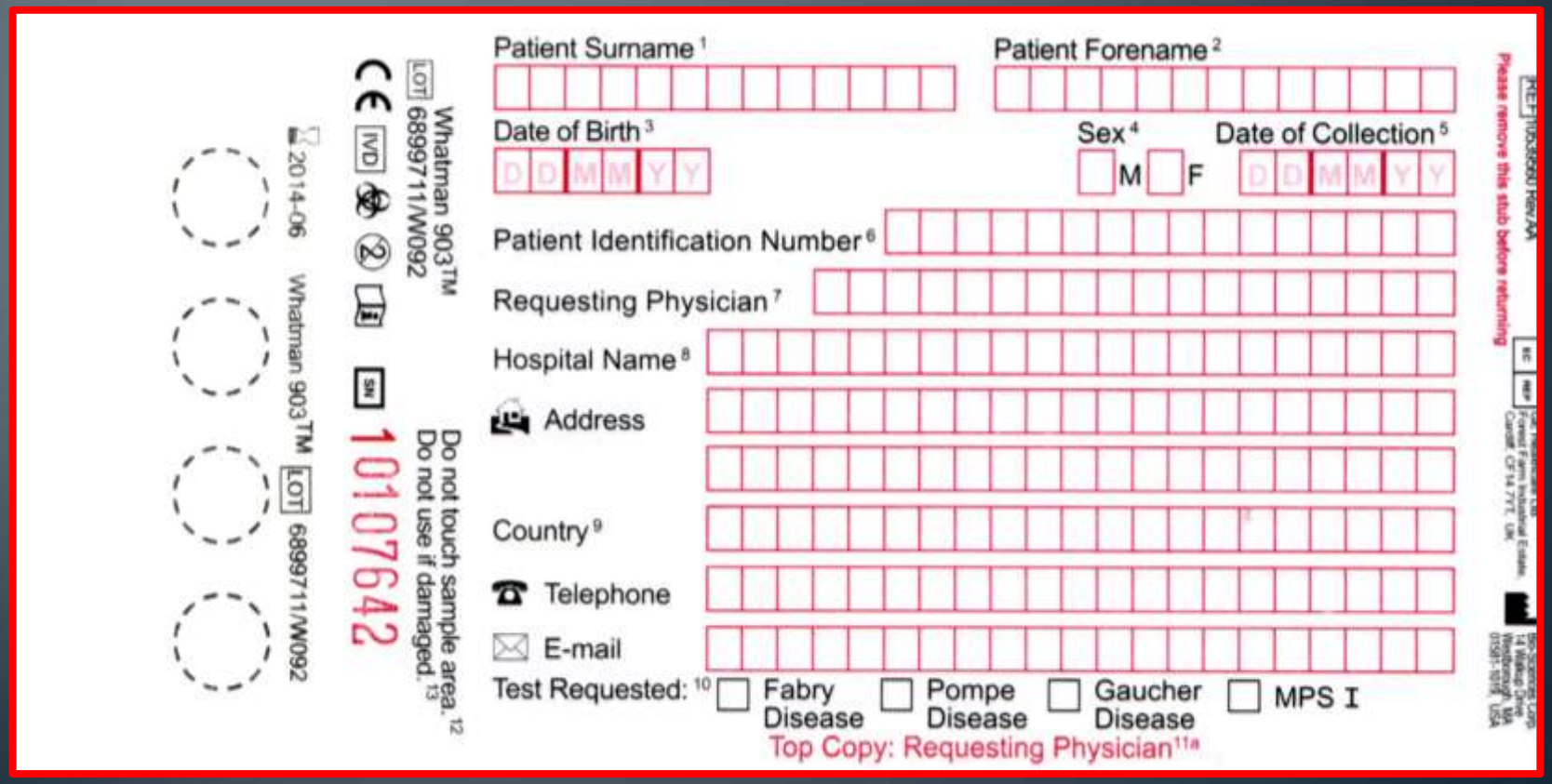
User Notes

MALS CENTRAL LAB
SEROGENETICS c/o DR TONY LANE 011 489 9221/0
ROOM 213, JAMES GEAR BUILDING

POMPES DISEASE TASK:1212182
SAMPLE: 2 x ACD TUBES ON ICE NOT FROZEN
MUST REACH LAB WITHIN 24HRS OF COLLECTION BEFORE 1500 MON-FRI
TURN AROUND TIME:10 WORKING DAYS
TEL #: MR IAIN SINCLAIR 489 9220 DR TONY LANE 489 9221

POMPE DISEASE
LABORATORY TESTING: GERMANY

- Dried Blood Spot (DBS): Hamburg Germany
  - Guthrie card – 4 spots: Genzyme



POMPE DISEASE
OVERVIEW OF MANAGEMENT

- Multi-system disorder ~ multidisciplinary team lead by physician with experience managing this disorder
  - Metabolic disease specialist/Biochemical geneticist (coordinate care)
  - Cardiologist
  - Pulmonologist/Respiratory therapist
  - Neurologist/Neuromuscular specialist/Physical therapist Occupational therapist/Audiologist/Speech therapist
  - Intensivist
  - Orthopaedist
  - Genetic counsellor
  - Metabolic dietician

POMPE DISEASE
CARDIOLOGY: COMMON ISSUES

- Cardiomyopathy:
  - HOCM -> increased LV mass. Hypertrophic and dilated CMO (Infantile-onset)
  - Late-onset: no clinically identifiable heart disease
- Heart failure
- Arrhythmia
  - Short PR interval: mechanism of accelerated AV conduction ~ to insulator effect of glycogen in the conduction tissue
  - True WPW can occur in Pompe disease
  - Conduction abnormalities + HOCM: high risk of tachyarrhythmia and sudden death (infection; fever; dehydration and anaesthesia)

POMPE DISEASE
CARDIOLOGY: COMMON ISSUES

- LVOT obstruction:
  - Digoxin; other inotropes; diuretics and afterload reducing agents ~ may exacerbate LVOTO (generally used in the later phase of disease: dilated CMO)
  - B-blockers to be used judiciously
  - Subendocardial ischaemia – risk for arrhythmia: avoid hypotension in diagnostic procedures requiring anaesthesia or where there is dehydration
  - ERT: reduction in cardiac mass

POMPE DISEASE
GENERAL MEDICAL CARE

- Due to overall hypotonia and respiratory muscle weakness ~ high risk for pneumonia -> respiratory failure; IPPV support and ventilator dependence and even death.
- Low threshold to treat infections
- Immunisations:
  - Seasonal Influenza vaccine (patients and household members)
  - Palivizumab (Synagis): during RSV season in infants and young children with Pompe disease
  - Pneumococcal vaccine (Prevenar)
    - After 2 years age and
    - Older patients who have not received it

POMPE DISEASE
SURGERY & ANAESTHESIA

- Safe anaesthesia a challenge in Infantile Pompe and HOCM – haemodynamic alterations
- Myocardial ischaemia and decreased cardiac output – not uncommon events
  - Thickened ventricular walls -> higher LVEDP at lower ventricular volumes -> increased potential for subendocardial ischaemia
- Halothane; Sevoflurane inhalation induction followed by Propofol infusion -> cause of intraop cardiac arrest
- Avoid intubation
- Group surgical procedures for single anaesthetic

POMPE DISEASE
SURGERY & ANAESTHESIA

- Peri-operative fluids: avoid hypovolaemia and avoid aggressive fluid management (high LVEDP ~ pulmonary oedema)
- Ketamine maintains SVR and contractility and is less likely to reduce preload.
- Etomidate: acceptable induction agent
- Propofol: afterload reduction and lower diastolic pressure may predispose to risk of myocardial ischaemia
- Underlying muscle weakness, more sensitive to neuromuscular blockade (Suxamethonium) -> rhabdomyolosis and hyperkalaemia
- Precautions for malignant hyperthermia

POMPE DISEASE
ENZYME REPLACEMENT THERAPY

- Infantile onset Pompe disease who receive ERT
  - Significantly prolongs survival
  - Decreases cardiomegaly and
  - Improves cardiac and skeletal muscle function
- Cardiac response appears to be good irrespective of stage of disease at start of ERT
- Skeletal muscle response – more variable than cardiac muscle. Best skeletal muscle response if ERT administered prior to skeletal muscle damage

POMPE DISEASE
ERT – ROLE OF CRIM STATUS

- CRIM (Cross Reactive Immunological Material) status – important predictor of clinical response
  - CRIM-negative patients are unable to make any *GAA* protein due to presence of underlying deleterious null *GAA* alleles ~ their immune system recognises rh*GAA* as a foreign protein and produce neutralising IgG antibodies to rh*GAA* rendering the treatment ineffective.
  - CRIM-positive patients produce some residual *GAA* protein , although non-functional inactive form. Typically have low anti-rh*GAA* antibody titres and better clinical outcome without the need for immunomodulation
  - Diagnosis of CRIM status--
    - *GAA* mutation analysis (turnaround time: Dukes 48-72 hours)
    - Addition of Western blot analysis in uncertain cases

POMPE DISEASE
ERT – ROLE OF CRIM STATUS

- CRIM-negative status: role of immunomodulation
  - Can be commenced prior to or shortly after commencing ERT
  - Immunomodulation Rx: effective in preventing an immune response in CRIM-negative patients who are naïve to ERT or who have had a short exposure to ERT
  - Attempts to eliminate antibodies in CRIM-negative patients who have been on ERT for an extended period with an entrenched immune response has failed
  - Delay in Rx in rapidly progressive disease like Infantile Pompe disease is detrimental to clinical outcome, thus methods for determining CRIM status needs to be rapid and accurate.

POMPE DISEASE
ERT – ROLE OF CRIM STATUS

- Immunomodulation
  - Successful immune tolerance induction with regimen of Rituximab (monoclonal antibody) + Methotrexate ± IVIG
  - Amount of immunomodulation required
    - Naïve patients
    - Receiving ERT – required prolonged immune modulation

POMPE DISEASE
ENZYME REPLACEMENT THERAPY

- Recombinant human acid α-glucosidase (rhGAA) derived from CHO cells
- Recommended dose 20 mg/kg body weight
- Administer as an intravenous (IV) infusion every two weeks

Myozyme [Summary of Product Characteristics]. Genzyme Europe B.V.; 2015.

POMPE DISEASE
GENETIC COUNSELLING & PRENATAL DIAGNOSIS

- Prenatal diagnosis
  - Measure enzyme activity in
  - Cultured amniotic fluid cells collected at 16/40 gestation ~ time consuming process as need to culture cells to produce sufficient material for probing
    - CVS: 10-12/40
      - Earlier diagnosis
      - Shorter time from biopsy to diagnostic report
      - Higher enzymatic activity of acid a-glucosidase in chorionic villi vs/ amniotic cells
      - Risk of contamination in CVS offset by doing DNA fingerprinting
  - Genotyping

POMPE DISEASE
ENZYME REPLACEMENT THERAPY

- Advent of ERT, natural history of this once fatal disease has been altered (ERT: 2006) South Africa: MCC registration 2012-2013
  - Physical and mental disabilities have been uncovered
- Unfavourable outcome despite early Rx
  - Muscle fibre type
  - Stage of disease at start of therapy
  - Genotype and
  - Immune response to recombinant enzyme
    - (CHO: Chinese hamster ovary cell-derived recombinant human acid alpha-glucosidase)

POMPE DISEASE
ENZYME REPLACEMENT THERAPY

- Clinical response to ERT varies considerably between patients
  - Age
  - Extent of muscle damage at initiation of ERT
  - Muscle fibre type
  - Defective autophagy
  - CRIM status – important predictor of clinical response
    - CRIM-negative patients are unable to make any *GAA* protein due to presence of underlying deleterious null *GAA* alleles ~ their immune system recognises rh*GAA* as a foreign protein and produce neutralising antibodies to rh*GAA* rendering the treatment ineffective.

POMPE DISEASE
CHALLENGES; UNASWERED QUESTIONS

- Palatal weakness
- Diaphragm weakness
- Loss of efficacy
- Affected carriers
  - Sensitivity/insensitivity of genotyping
- Logistics
  - CRIM status before commencing Rx elsewhere in world (not so in South Africa)