Evidence-Based Medicine: Diagnostic study

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What is Evidence-Based Medicine (EBM)?

“Expertise in integrating
1. Best research evidence
2. Clinical Circumstance
3. Patient values
in clinical decisions”

Haynes, Devereaux, & Guyatt, 2002
What are “tests” used for?

Log of reasons by several docs:
- Diagnosis – most common but also
- Monitoring – has it changed?
- Prognosis – risk/stage within Dx
- Treatment planning, e.g., location
Gold/Reference standard

Indication of TRUTH (whether the disease is truly present or not)

Test

Try to estimate the truth. Find the best guess !! Feasibility, cost, safety

Diagnostic test

Tests with Dichotomous results
Positive or Negative

Tests of Continuous variables
## Accuracy of a Test Result

<table>
<thead>
<tr>
<th>TEST</th>
<th>DISEASE</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>True positive</td>
<td>(a)</td>
<td>False positive</td>
</tr>
<tr>
<td>Negative</td>
<td>False negative</td>
<td>(c)</td>
<td>True negative</td>
</tr>
</tbody>
</table>

\[
\text{Sensitivity} = \text{true positive rate} = \frac{a}{a + c} \\
\text{Specificity} = \text{true negative rate} = \frac{d}{b + d}
\]

---

**Test results for two patient populations with different cut off value**

- **Brain natriuretic peptide (BNP)**
- And
- **Systemic Inflammatory Response Syndrome (SIRS)**
### Table 1: CK Levels and Infarct Status

<table>
<thead>
<tr>
<th>Infarct Present</th>
<th>CK</th>
<th>Infarct Absent</th>
<th>CK</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 15%</td>
<td>480+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8 3%</td>
<td>440</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7 3%</td>
<td>400</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15 8%</td>
<td>360</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>19 8%</td>
<td>320</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>13 6%</td>
<td>280</td>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td>18 8%</td>
<td>240</td>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td>19 8%</td>
<td>200</td>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td>21 9%</td>
<td>160</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30 13%</td>
<td>120</td>
<td>5</td>
<td>4%</td>
</tr>
<tr>
<td>36 13%</td>
<td>80</td>
<td>130</td>
<td>67%</td>
</tr>
</tbody>
</table>

### Table 2: Rule in/Out

<table>
<thead>
<tr>
<th>Infarct Present</th>
<th>CK</th>
<th>Infarct Absent</th>
<th>CK</th>
</tr>
</thead>
<tbody>
<tr>
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<td>5</td>
<td>4%</td>
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<tr>
<td>36 13%</td>
<td>80</td>
<td>130</td>
<td>67%</td>
</tr>
</tbody>
</table>

### Percentages

- **True+**: 93%
- **False-**: 6%
- **False+**: 12%
- **True-**: 83%
- **Rule in**: 42%
- **Rule out**: 1%

Note: CK levels are grouped into categories: 0, 40, 80, 120, 160, 200, 240, 280, 320, 360, 400, 440, 480+.
Sensitivity
- The ability of test to identify correctly those who have the disease.
- Use to “rule out”
- There is a reason to suspect a dangerous but treatable condition

Specificity
- The ability of the test to identify correctly those who do not have the disease
- Use to confirm “rule in”
- Need when false-positive results can harm the patient physically, emotionally, or financially.

Receiver Operating Characteristic curve

Very good
Good
Flip a coin instead
Predictive Value of a Test Result

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>True positive</td>
<td>False positive</td>
</tr>
<tr>
<td>Negative</td>
<td>False negative</td>
<td>True negative</td>
</tr>
<tr>
<td></td>
<td>$a + b$</td>
<td>$c + d$</td>
</tr>
</tbody>
</table>

Pre-test probability or Prevalence of disease = $\frac{a + c}{a + b + c + d}$

Then

Positive predictive value = $\frac{a}{a + b}$

Negative predictive value = $\frac{d}{c + d}$

2 by 2 table: 

<table>
<thead>
<tr>
<th>Test</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>+</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Positive predictive value

Sensitivity

Pre-test probability or Prevalence of disease
Pre-test probability

- The probability of disease before the test result is known
- Prevalence

What are the problems with predictive values?
### Example 1: Screening in homosexuals

<table>
<thead>
<tr>
<th>ELISA</th>
<th>Western BLot</th>
<th>Antibodies</th>
<th>No Ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive</td>
<td>498</td>
<td>4</td>
<td>502</td>
</tr>
<tr>
<td>negative</td>
<td>10</td>
<td>c</td>
<td>488</td>
</tr>
</tbody>
</table>

**Prevalence of disease** = \( \frac{508}{1000} = 50.8\% \)

**Sensitivity** = \( \frac{498}{508} = 98\% \)

**Specificity** = \( \frac{488}{492} = 99\% \)

**PPV** = \( \frac{498}{502} = 99\% \)

**NPV** = \( \frac{492}{498} = 98\% \)

### Example 2: Screening in blood donors

<table>
<thead>
<tr>
<th>ELISA</th>
<th>Western BLot</th>
<th>Antibodies</th>
<th>No Ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive</td>
<td>1960</td>
<td>7984</td>
<td>9944</td>
</tr>
<tr>
<td>negative</td>
<td>40</td>
<td>c</td>
<td>990,016</td>
</tr>
</tbody>
</table>

**Prevalence of disease** = \( \frac{2000}{1,000,000} = 0.2\% \)

**Sensitivity** = \( \frac{1960}{2000} = 98\% \)

**Specificity** = \( \frac{990,016}{998,000} = 99\% \)

**PPV** = \( \frac{1960}{9944} = 19.7\% \)

**NPV** = \( \frac{990019}{1000000} = 99.9\% \)
Predictive values

Anti HIV positive
เป็นจริงๆหรือคะ

Negative
ไม่เป็นแน่นะคะ

PPV
NPV

Likelihood ratios

- Use to describing the performance of a diagnostic test.
- Summarize the same kind of information as sensitivity and specificity.

Advantages:
- Calculate the post-test probability
- Use in multiple levels of test
- Not effect by prevalence
Likelihood ratio of a positive test \( LR^+ \)

- Ratio of a **positive test result** among diseased to the same result in the “healthy”
- Ratio of the probability of a **true positive** result if the disease is present to a **false positive** result if the disease is absent.

\[
LR^+ = \frac{a}{a+c}/\left(\frac{b}{b+d}\right) = \frac{Sen}{1-Spec}
\]

Express how many times more likely a **test positive** is to be found in diseased, compared with nondiseased people.

Likelihood ratio of a negative test \( LR^- \)

- Ratio of a **negative result** among diseased to the same result in the “healthy”
- Ratio of the probability of a **false negative** result if the disease is present to the probability of a **true negative** result if the disease is absent.

\[
LR^- = \frac{c}{a+c}/\left(\frac{d}{b+d}\right) = \frac{1-Sen}{Spec}
\]

Express how many times less likely a **test negative** is to be found in diseased, compared with nondiseased people.
Probability vs. Odds

- Probability (P)
  - The proportion of people in whom a particular characteristic, such as a positive test, is present.

- Odds
  - The ratio of two probabilities of an event to that of 1-the probability of the event

\[
\text{Odds} = \frac{P}{1-P} \quad \text{or} \quad \frac{P}{1+\text{Odds}}
\]

Example

- Probability of win = 0.8

- Odds of win
  \[
  = \frac{0.8}{1-0.8} = \frac{0.8}{0.2} = 4
  \]
Mathematical approach

1) Convert pretest probability (prevalence) to pretest odds
Pretest odds = prevalence/(1-prevalence) = 0.5/(1-0.5) = 1

2) Multiply pretest odds by LR to obtain posttest odds
Pretest odds x LR = posttest odds
1 x 10 = 10

3) Convert posttest odds to posttest probability
Posttest probability = posttest odds/(1+posttest odds) = 10/(1+10) = 0.90 = 90%

How much do Likelihood Ratios change disease likelihood?

<table>
<thead>
<tr>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>5-10</td>
<td>0.1-0.2</td>
</tr>
<tr>
<td>2-5</td>
<td>0.2-0.5</td>
</tr>
<tr>
<td>&lt;2</td>
<td>&gt;0.5</td>
</tr>
</tbody>
</table>

Large changes
Moderate changes
Small changes
Little or no change
Fagan Nomogram

Multiple tests

Parallel testing

Test A or Test B or Test C is positive

\[
\begin{align*}
A & \rightarrow + \\
B & \rightarrow + \\
C & \rightarrow + \\
\end{align*}
\]

Consequence  \[\text{Sensitivity}\]
\[\text{Specificity}\]
Multiple tests

Serial testing
Test A and Test B and Test C are positive

\[ A \rightarrow + \ B \rightarrow + \ C \rightarrow + \]

Consequence

Sensitivity

Specificity

Diagnostic odds ratio DOR

- The ratio of the odds of positivity in disease relative to the odds of positivity in the nondiseased.

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Disease</td>
</tr>
<tr>
<td>positive</td>
<td>TP</td>
</tr>
<tr>
<td>Negative</td>
<td>FN</td>
</tr>
</tbody>
</table>
**Diagnostic odds ratio (DOR)**

\[
DOR = \frac{TP}{FN} \div \frac{FP}{TN}
\]

\[
= \frac{sens}{(1-sens)} \div \frac{(1-spec)}{spec}
\]

\[
= \frac{PPV}{(1-PPV)} \div \frac{(1-NPV)}{NPV}
\]

\[
= \frac{LR+}{LR-}
\]

**How do we actually practice EBM?**

**5 A’s of EBM**

- Step 1: Ask answerable question
- Step 2: Find an Article
- Step 3: Critical Appraisal the evidence
- Step 4: Apply
- Step 5: Assess
Clinical Scenario

• A 67-year-old woman was found to have HT 12 years ago.
• Her blood pressure is uncontrolled in last year of follow-up even 4 anti-hypertensive agents were prescribed.
• Her SBP is around 200 mmHg, and her diastolic blood pressure is around 100 mmHg.
• A dipstick test shows proteinuria ++.
• Her serum creatinine is 1.67 mg/dl (eGFR 31).

Clinical Scenario

• You wonder this patient may have renal artery stenosis and ischemic nephropathy.
• You ask your advisor and he suggested to perform MRA.
• But you think about CTA.
4 parts of clinical question

- **Patient or Problem** P
- **Intervention or exposure** I
- **Comparison** C
- **Outcome** O

**Patient**
- In a 67-year-old woman with uncontrolled hypertension

**Intervention or Exposure**
- MR angiography

**Comparison**
- CT angiography

**Outcome**
- Diagnosis of renal artery stenosis
Patient
  ▫ In a 67-year-old woman with uncontrolled hypertension

Intervention or Exposure
  ▫ MR angiography

Comparison
  ▫ CT angiography

Outcome
  ▫ Diagnosis of renal artery stenosis

How do we actually practice EBM?
5 A’s of EBM
  • Step 1: Ask answerable question
  • Step 2: Find an Article
  • Step 3: Critical Appraisal the evidence
  • Step 4: Apply
  • Step 5: Assess
How to choose the right article(s)?
How to choose the right article(s)?

- Relevant
  - P
  - I
  - C
  - O
- High impact factor journal
- Up date
- Well-known authors
How do we actually practice EBM?

5 A’s of EBM

- Step 1: Ask answerable question
- Step 2: Find an Article
- Step 3: Critical Appraisal the evidence
- Step 4: Apply
- Step 5: Assess

Users’ Guide for an Article About Interpreting Diagnostic Test Results

Guyatt GH, Rennie D. Users’ guides to the medical literature. 2002
Critical appraisal

- Are the results of the study valid?
- What are the results?
- How can you apply the results to patient care?

Are the results valid?

- 1. Did participating patients present a diagnostic dilemma?

```
<table>
<thead>
<tr>
<th>Disease</th>
<th>Test</th>
<th>No disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncontrolled HT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal bruit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cr rising after ACEI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal population</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
```

Medium clinical suspicious
Pre-test probability

- The probability of disease before the test result is known
- Prevalence

Are the results valid?

- 1. Did participating patients present a diagnostic dilemma?
Participants
Over a 3-month period, patients were prospectively recruited from the internal medicine outpatient clinics of 3 large teaching hospitals and 3 university hospitals in the Netherlands. The ethical review board of each hospital approved the study, and written informed consent was obtained from all participants. At the 2 hospitals that recruited most of the participating patients, enrollment was consecutive; the other participating hospitals included patients by using nonrandomized case-control samples. A total of 25 participating centers, all hypertensive patients between 18 and 75 years of age with a diastolic blood pressure greater than 90 mm Hg were randomly selected for predefined clinical cases indicating renal artery stenosis, as described in the Working Group on Renovascular Hypertension (15) and others (16, 17). Patients were eligible for participation in the study if their exhibited at least 1 clinical parameter consistent with atherosclerotic renal artery stenosis and pregnancy contraindicated MRA, CTA, or DSA. 0% communications to interventions or previous participation in the study. All included patients were scheduled to have CTA, MRA, and DSA within a 3-month period. All participating patients were informed about the study, and written consent was obtained before enrollment. The study was approved by the ethical review board of each participating center.

Methods
The study was conducted at 2 participating centers, all with experience in percutaneous coronary interventions. All examinations were performed by experienced interventional radiologists using the same equipment and protocols. The mean time from the last injection of contrast material to the start of the examination was 30 minutes. The examination included DSA of the renal arteries, CTA of the abdominal aorta, and MRA of the renal arteries. The DSA images were acquired using a digital subtraction angiography system (General Electric Healthcare, Milwaukee, WI) with a 64-slice helical CT scanner (Siemens, Erlangen, Germany). The CTA images were acquired using a 64-slice helical CT scanner (Siemens, Erlangen, Germany) with a collimation of 0.6 mm, a pitch of 0.6, and a rotation time of 0.5 seconds. The MRA images were acquired using a 3.0-Tesla MRI scanner (Philips Healthcare, Best, The Netherlands) with a 6-channel phased-array coil. The images were acquired with a 3D time-of-flight technique using a 32-slice helical CT scanner (Siemens, Erlangen, Germany), with a collimation of 0.6 mm, a pitch of 0.6, and a rotation time of 0.5 seconds. The examination included DSA of the renal arteries, CTA of the abdominal aorta, and MRA of the renal arteries. The DSA images were acquired using a digital subtraction angiography system (General Electric Healthcare, Milwaukee, WI) with a 64-slice helical CT scanner (Siemens, Erlangen, Germany). The CTA images were acquired using a 64-slice helical CT scanner (Siemens, Erlangen, Germany) with a collimation of 0.6 mm, a pitch of 0.6, and a rotation time of 0.5 seconds. The MRA images were acquired using a 3.0-Tesla MRI scanner (Philips Healthcare, Best, The Netherlands) with a 6-channel phased-array coil. The images were acquired with a 3D time-of-flight technique using a 32-slice helical CT scanner (Siemens, Erlangen, Germany), with a collimation of 0.6 mm, a pitch of 0.6, and a rotation time of 0.5 seconds.
Are the results valid?

- 2. Did investigators compare the test to an appropriate, **independent reference standard**?

---

**Gold/Reference standard**

Indication of TRUTH (whether the disease is truly present or not)

**Test**

Try to estimate the truth. Find the best guess!!
Feasibility, cost, safety
Are the results valid?

- 2. Did investigators compare the test to an appropriate, **independent reference standard**?

> “Truth should be achieved without sacrificing the patients”

---

**Gold standard**

- Acceptable?
- The test **should not** be a part of the gold standard – inflate diagnostic power

```
Test 1
Test 2
Test 3
Gold standard = Test1 + Test 2 + Test 3
```
Are the results valid?

- 3. Were those interpreting the test and reference standard **blind** to the other results?

---

**Independent: Blinding**

- Independent reading

![Diagram showing independent reading with test, gold standard, interpreter 1, and interpreter 2 with an awareness gap between them]
“If there is no blinding”

CT angiography → Renal artery cath.

Imaging Techniques

Each participating hospital was equipped with state-of-the-art magnetic resonance scanners (1.0 or 1.5 Tesla), helical computed tomography scanners (single or multidetector row systems), and DSA equipment. In addition, hospitals were allowed to optimize scan protocols during the study. New insights emerged as when equipment was upgraded, an approach that conforms to usual clinical practice. Changes in scan protocols occurred rarely (Appendix Table 1, available at www.urine.org). To ensure state-of-the-art magnetic resonance imaging, all scan protocols had to meet minimal quality standards in terms of spatial resolution and scan duration. The quality standards were defined by the coordinating center and were based on the protocols that were published at the start of the study. During the entire study, the coordinating center continuously monitored the quality of all images.

Information about manufacturers, scan protocols, and equipment is shown in Appendix Table 1 (available at www.urine.org). All imaging was performed or supervised by experienced radiologists and radiologic technologists. Renal CTA, MRA, and DSA had already been part of the daily routine before the start of the study.

Each method had more than 6 years of experience. Each observer independently performed the evaluation and was blinded to all other results, including clinical information and DSA results. Digital image data for all networks were acquired by the same workstation, equipped with all available tools used image-processing software (GanVision, release 4.2.1, Philips Medical Systems, Best, the Netherlands). Source images had to be examined in all cases before a final diagnosis could be made.

The DSA images were evaluated by 8 vascular radiologists, all with more than 10 years of experience in this particular field. The first observer was the radiologist who actually performed the test; the evaluation took place during the DSA procedure. The second and third observers who judged each DSA examination knew the first observer’s judgment. If discrepancies existed among the first 3 observers with respect to the number of renal arteries involved or the nature, location, or severity of disease, differences of >10% in the degree of stenosis, a fourth radiologist, who had access to the diagnosis of the other observers, made the final diagnosis. This consensus approach has been used in previous CT and MRA studies (6, 7, 13–14). All DSA observers were blinded to the results of CTA and MRA.
Are the results valid?

- 4. Did investigators perform the same reference standard to all patients regardless of the results of the test under investigation?

**Verification bias** or **“work-up bias”**

```
Test
  Positive
  Negative
```

```
<table>
<thead>
<tr>
<th>Test</th>
<th>Positive</th>
<th>Gold standard</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
```
Are the results valid?

- Dx uncertainty: spectrum of disease?
- Blind comparison: test vs. independent gold standard?
- Verification bias: if positive test, then proceed gold standard?

Valid?

If so, we proceed......!
What are the results?

• What **likelihood ratios** were associated with the range of possible test results?
  ▫ Estimates:
    • sensitivity, specificity
    • Predictive values
    • Likelihood ratios
    • Diagnostic odds ratio
  ▫ Precision: 95% CI
Likelihood ratio

- CTA
  \[ LR^+ = \frac{0.64}{1 - 0.92} = 8.0 \]
  \[ LR^- = \frac{1 - 0.64}{0.92} = 0.4 \]

- MRA
  \[ LR^+ = \frac{0.62}{1 - 0.84} = 3.8 \]
  \[ LR^- = \frac{1 - 0.62}{0.84} = 0.5 \]
How can I apply the results to patient care?

1. Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?
   ▫ Variation of test
   ▫ Variation of interpretation
   ▫ Ability to diagnose

2. Are the results applicable to the patient in my practice?
   ▫ Disease severity
     ▪ Severe disease: LR move away from 1
     ▪ Mild disease: LR move toward 1
   ▫ Practice: setting
   ▫ Patients: meet inclusion & exclusion criteria
How can I apply the results to patient care?

- 3. Will the results change my management strategy?
  - The treatment threshold (start treatment)

Scenario

- A 28-year-old man
  - Normal BP
- A 78-year-old woman
  - Uncontrolled HT, DM

Probability of renal artery stenosis

Pretest probability
Pretest probability

- A 28-year-old man
- Normal BP
- A 78-year-old woman
- Uncontrolled HT, DM

Probability of renal artery stenosis

Pretest probability

Low

High

Posttest probability

- A 28-year-old man
- Normal BP
- A 78-year-old woman
- Uncontrolled HT, DM

Probability of positive CT angiography

Pretest probability of renal artery stenosis

Low

High

Posttest probability of renal artery stenosis

??
Likelihood Ratio (LR)

- A 28-year-old man
- Normal BP
- A 78-year-old woman
- Uncontrolled HT, DM

Pretest probability of renal artery stenosis

Probability of positive CT angiography

Posttest probability of renal artery stenosis

Fagan Nomogram

LR

Low

Pretest probability

High

LR

Postest probability

Large impact

Moderate impact

Small impact

Moderate impact

Large impact
How can I apply the results to patient care?

• 4. Will patients be better off as a result of the test?
  ▫ Benefit
  ▫ Risk
  ▫ Cost

EBM AS A CYCLE

Decision

Clinical Question

Clinical circumstance and patient values

Systematic search for best evidence

Assessment of applicability

Assessment of validity
Case scenario

- A Thai 28 year-old-man from Lampang
- Occupation: driver
- **Chief complaint:** prolonged fever for 2 months
- **Present illness:**
  - 2 month PTA - intermittent low grade fever with headache, no cough, no dyspnea
  - 1 month PTA - low grade fever with malaise, dyspnea on exertion, orthopnea, PND, polymyalgia
Case scenario

- 2 week PTA low grade fever with chest pain, progressive dyspnea; functional class change from class II ---> class III, PND, orthopnea, anorexia, significant weight loss: 67 kg ---> 60 kg in 2 month

Physical examination

General appearance

- A Thai young man, full consciousness, mild pale, no jaundice, well cooperator, oriented to time/place/person

vital sign: Temp. 38.8 C BP 110/60 mmHg PR 110 bpm respiratory rate 24 /min

HEENT: multiple dental carries

No Roth’s spot, no splinter hemorrhage, no Osler’s node, no Janeway’s lesion
Physical examination

Respiratory: tachypnea, dyspnea with accessory muscle used, good air entry, fine crepitation in both lower lung zone

Cardiovascular:
- no central and peripheral cyanosis
- Full, regular, symmetrical pulse at all extremities
- PMI at 6th ICS, lateral to midclavicular line, active precordium, thrill at LUSB and LLSB
- systolic ejection murmur at LSB grade III, diastolic blowing murmur grade III at LUSB

You wonder whether you should sent him to perform
- Transesophageal Echocardiography (TEE)
or
- Transthoracic Echocardiography (TTE) for infective endocarditis diagnosis