

# Challenges in the diagnosis of heparin-induced thrombocytopenia

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# Diagnostic testing answers clinical questions

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## **Diagnostic questions**

- Ruling-in diseases
- Ruling-out diseases
- Screening for disorders



## **Prognostic questions/ prediction**

- Risk factors
- Prediction of future events
- Staging of cancer



## **Monitoring**

- Effectiveness of treatment
- Safety of treatment
- Course of disease

Do we know the performance of diagnostic tests?

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*What does the test result mean for my patient?*

## Do we know the performance of diagnostic tests?

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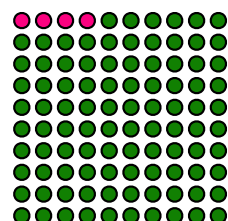


*What does the test result mean for my patient?*

## Performance of diagnostic tests in real-life practice

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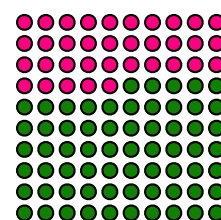
Manufacturer



Total=100

Real-life practice

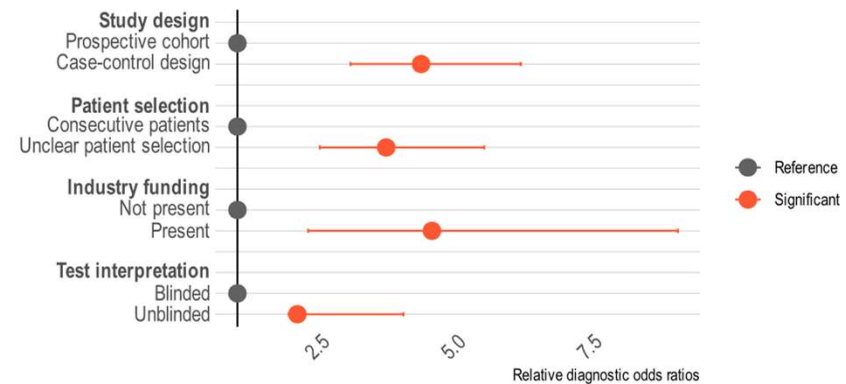
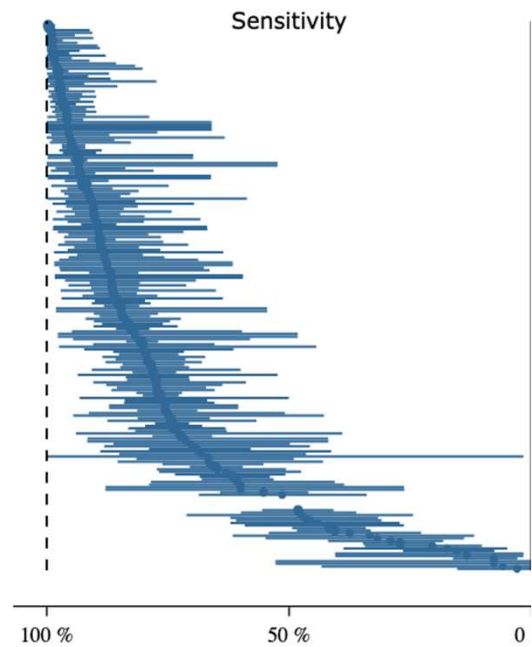
■ True positives  
■ False negatives



Total=100

Considering a proportion of positive tests of 5.8% would result in 8'454 correctly identified with a SARS-CoV-2 infection but 4'493 individuals falsely classified as SARS-CoV-2 negative.

# Why most studies overestimate test performance

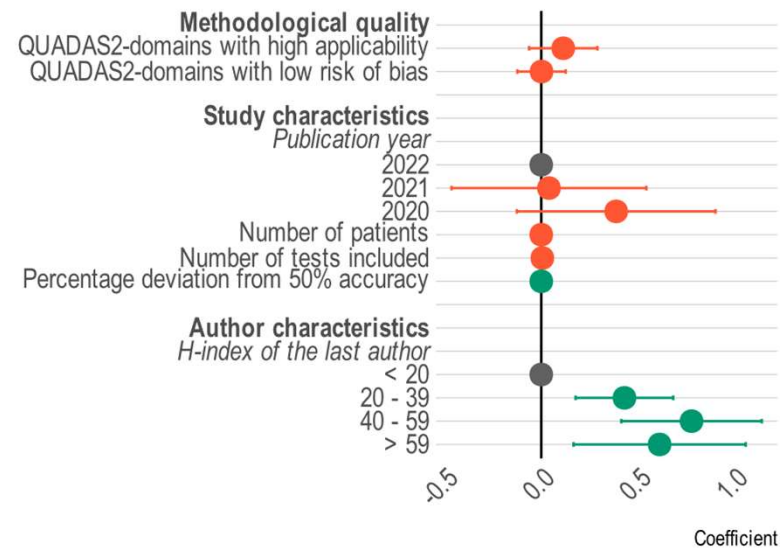


*Submitted for publication*

# Determinants of publication success

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## A. Impact factor 2020

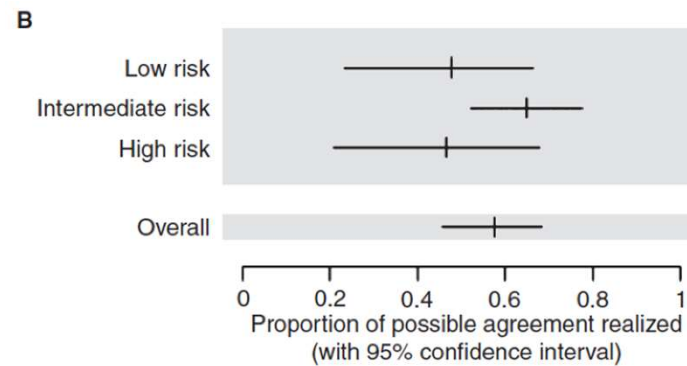


Submitted for publication



## Reproducibility of the 4Ts score

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# Performance of the 4Ts score in clinical practice

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## CLINICAL TRIALS AND OBSERVATIONS

### **Combination of 4Ts score and PF4/H-PaGIA for diagnosis and management of heparin-induced thrombocytopenia: prospective cohort study**

Lori-Ann Linkins,<sup>1,2</sup> Shannon M. Bates,<sup>1,2</sup> Agnes Y. Y. Lee,<sup>3</sup> Nancy M. Heddle,<sup>1</sup> Grace Wang,<sup>1</sup> and Theodore E. Warkentin<sup>4</sup>

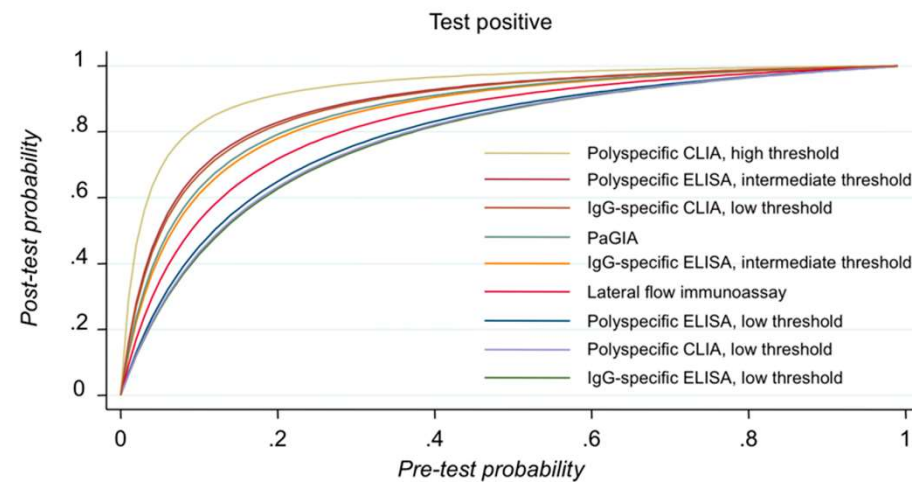
<sup>1</sup>Department of Medicine, McMaster University, Hamilton, ON, Canada; <sup>2</sup>Thrombosis & Atherosclerosis Research Institute, Hamilton, ON, Canada; <sup>3</sup>Division of Hematology, University of British Columbia, Vancouver, BC, Canada; and <sup>4</sup>Department of Pathology and Molecular Medicine, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, ON, Canada

*Sensitivity of the 4T's score in clinical practice: 80-90 %*

*J Thromb Haemost* 2012; 10: 151–2.; *J Crit Care*. 2014 Dec;29(6):1126-7; *Blood*. 2015;126(5):597-603; *Blood*. 2015 Jul 30;126(5):563-4

## Consistency of H/PF4 Antibody assays

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*Blood. 2016;127(5):546-557; 2023 J Thromb Haemost; 2016 PLoS ONE 12(6): e0178289*

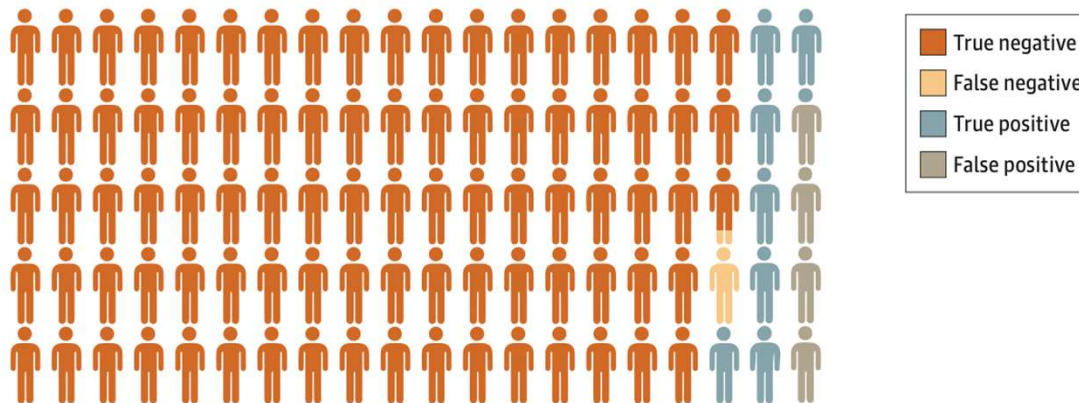


Original Investigation | Hematology

## Accuracy of Diagnosing Heparin-Induced Thrombocytopenia

Emil List Larsen, MD, PhD; Henning Nilius, MD; Jan-Dirk Studt, MD, PhD; Dimitrios A. Tsakiris, MD; Andreas Greinacher, MD; Adriana Mendez, MD; Adrian Schmidt, MD; Walter A. Willemin, MD, PhD; Bernhard Gerber, MD; Prakash Vishnu, MD; Lukas Graf, MD; Johanna A. Kremer Hovinga, MD; Jens P. Goetze, MD, DMSc; Tamam Bakchoul, MD; Michael Nagler, MD, PhD

### C Recommended diagnostic algorithm



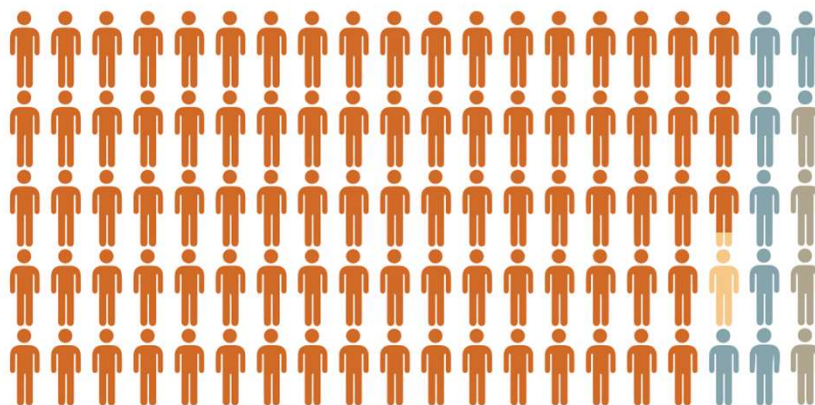


Original Investigation | Hematology

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### **C** Recommended diagnostic algorithm



## NEJM Journal Watch

GENERAL MEDICINE SPECIALTIES TOPICS VOICES CME GUIDELINE WATCH

SUMMARY AND COMMENT | GENERAL MEDICINE, HOSPITAL MEDICINE, ONCOLOGY AND HEMATOLOGY

INFORMING PRACTICE

April 11, 2024

### Diagnosing Heparin-Induced Thrombocytopenia: How Accurate Is the Recommended Algorithm?

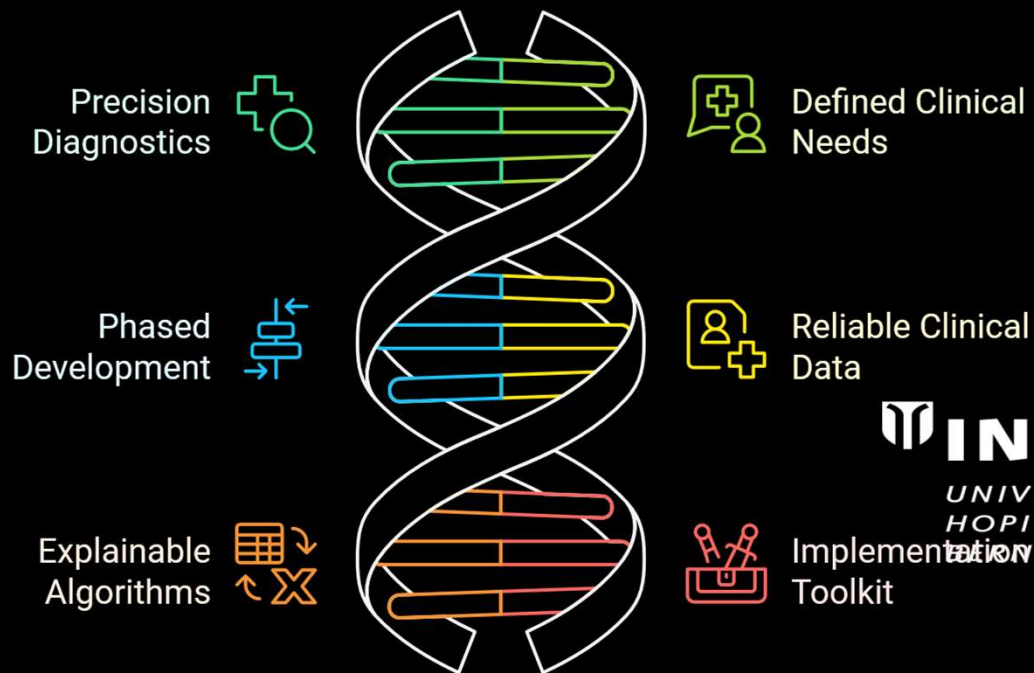
Daniel D. Dressler, MD, MSc, MHM, FACP, reviewing Larsen EL et al. JAMA Netw Open 2024 Mar

*Sensitivity and specificity were high, but a small proportion of patients assessed as low risk might deserve further testing.*

Heparin-induced thrombocytopenia (HIT) is a high-risk condition that requires immediate therapy with high-risk medications; thus, accurate diagnosis is critical. Because HIT-antibody testing has a relatively high false-positive rate, guidelines direct clinicians to use an algorithm that starts with the 4Ts score and then recommends antibody testing in patients whose 4Ts scores indicate intermediate or high risk for HIT. In this prospective study of 1300 patients with possible HIT, investigators assessed the accuracy of the 4Ts score and the guideline-recommended diagnostic algorithm. The reference-standard test for comparison was a heparin-induced platelet activation assay; prevalence of HIT was 8.4% by reference-standard testing.

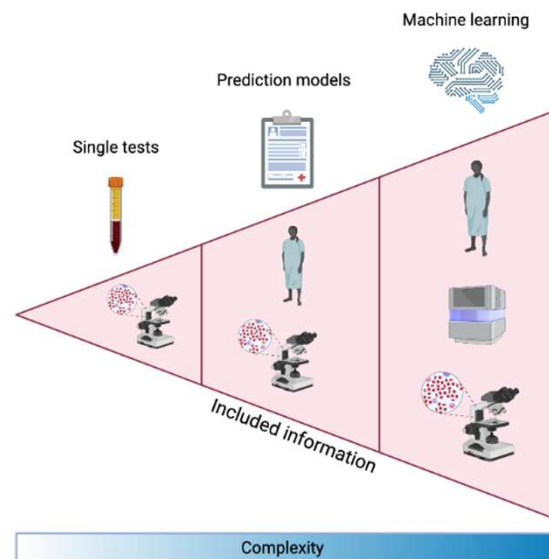
Positive predictive values of 4Ts score and the recommended diagnostic algorithm were expectedly low (15% and 66%, respectively). However, nearly half of patients were low risk using 4Ts score and would not have warranted antibody testing by the recommended diagnostic algorithm. That algorithm had high sensitivity (87%) and specificity (96%) and a very high negative predictive value (99%).

# Essentials of Diagnostic Innovation



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## What can we do?



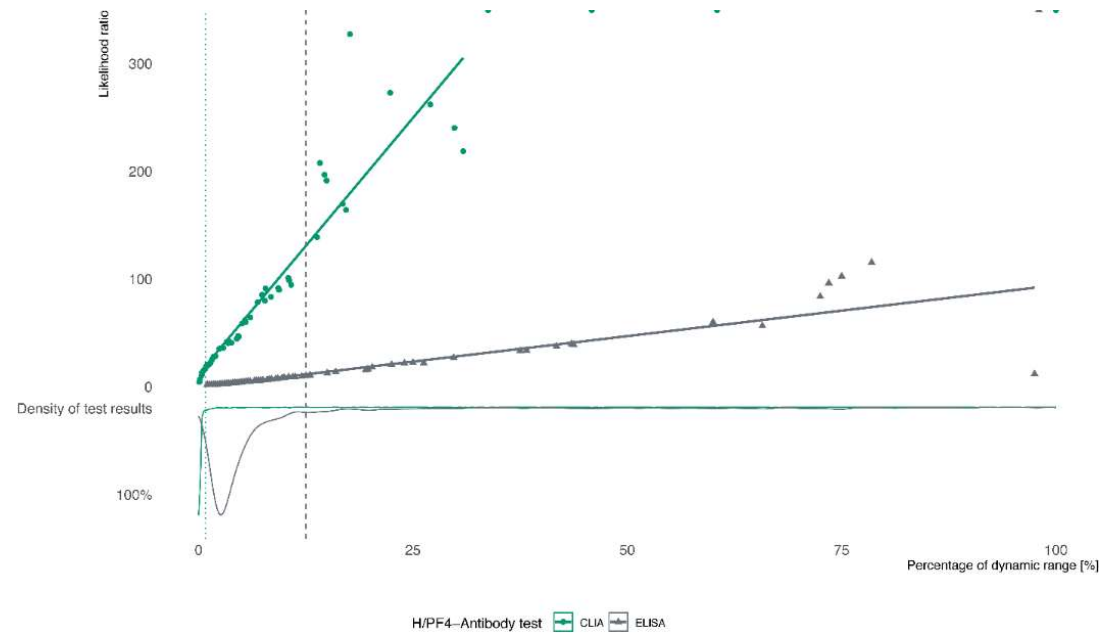
*Integrating more diagnostic  
information*

*Rigorously designed clinical studies*

Am J Haematol. 2023 Sep;202(5):925-927; Pol Arch Intern Med. 2024 Aug 8;134(7-8):16772; J Transl Autoimmun. 2022 Mar 6;5:100151

## Dynamic range of H/PF4 Antibody assays

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*Major revision in process*

## Dynamic range of H/PF4 Antibody assays

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**Pre-test probability**  
According to the 4Ts score ▼

**4Ts Score result**  
Intermediate 4Ts score (4-5) ▼

**Type of immunoassay**  
Acustar HIT-IgG (CLIA) [U/mL] ▼

**Result in U/ml**  
1.30 - 3.09 ▼

Calculate probability



*Major revision in process*

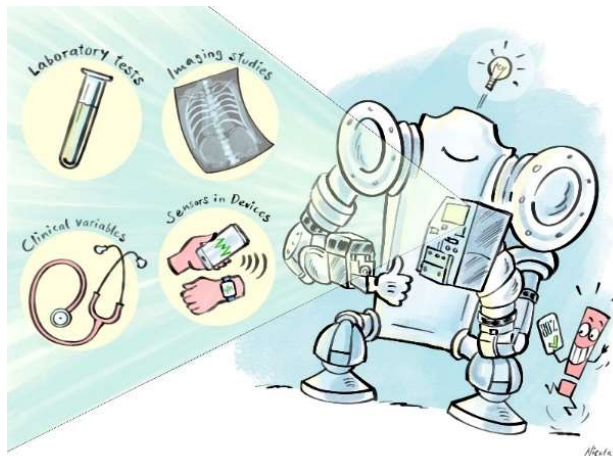
## Other Bayesian Algorithms (Lorenzo Alberio)

| 1 <sup>st</sup> step<br>Assess HIT pre-test probability with the 4T score                                                                                                                                                           | 2 <sup>nd</sup> step<br>CLIA HIT-IgG testing in patients with a 4T score ≥2 (and/or with unexplained heparin resistance) |                                     |                       | 3 <sup>rd</sup> step<br>PaGIA-H/PP4 testing in patients with CLIA HIT-IgG results in the intermediate "grey-zone" (0.13-3.0 U/ml) | 4 <sup>th</sup> step<br>Assess the individual post-test probability for HIT |                          |                          | 5 <sup>th</sup> step<br>Clinical decision (expected patients, %)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|-------------------------------------|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|--------------------------|--------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Result (score)                                                                                                                                                                                                                      | Result (U/ml)                                                                                                            | Likelihood ratio (95% CI in Tab. 2) | Expected patients (%) | Result (titre)                                                                                                                    | Low 4T score P (95% CI)                                                     | Int. 4T score P (95% CI) | High 4T score P (95% CI) |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Pre-test probability for HIT according to 4T score:</b> <sup>15,29</sup><br>0-3: Low (<1%)<br>4-5: Int (10-14%)<br>6-8: High (50-64%)<br><br><b>Proposed approach:</b><br>0-1 : HIT ruled out *<br>≥ 2 : ad 2 <sup>nd</sup> step | <0.13                                                                                                                    | LR 0.00                             | 70-80                 | --                                                                                                                                | 0%                                                                          | 0% (0-3)                 | 0% (0-25) ††             | <b>≤3% post-test probability for HIT :</b><br>HIT ruled out,<br>Continue heparin<br><b>(Expected scenario in up to 90% of cases)</b><br><br><b>Undetermined post-test probability for HIT:</b><br>Perform HIPA functional assay as diagnostic gold- standard.<br>While result pending, manage according to clinical judgment<br><b>(Expected scenario in ≤5% of cases)</b><br><br><b>≥75% post-test probability for HIT :</b><br>HIT ruled in,<br>Stop heparin,<br>Start alternative anticoagulant therapy<br><b>(Expected scenario in 5-10% of cases)</b> |
|                                                                                                                                                                                                                                     | 0.13-<0.33 †                                                                                                             | LR 0.60                             | 10-20                 | ≤1                                                                                                                                | 0%                                                                          | 0% (0-2)                 | 0% (0-17)                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                     |                                                                                                                          |                                     |                       | 2                                                                                                                                 | 0%                                                                          | 3% (0-18)                | 24% (4-70)               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                     |                                                                                                                          |                                     |                       | 4                                                                                                                                 | 0% (0-1)                                                                    | 29% (13-53)              | 82% (63-92)              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                     |                                                                                                                          |                                     |                       | 8                                                                                                                                 | 4% (1-12)                                                                   | 76% (41-93)              | 97% (88-99)              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                     |                                                                                                                          |                                     |                       | ≥16                                                                                                                               | 100% (2-100)                                                                | 100% (70-100)            | 100% (96-100)            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                     | 0.33-<1.0 ‡                                                                                                              | LR 3.40                             |                       | ≤1                                                                                                                                | 0%                                                                          | 0% (0-9)                 | 0% (0-53)                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                     |                                                                                                                          |                                     |                       | 2                                                                                                                                 | 0%                                                                          | 14% (2-55)               | 65% (20-93)              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                     |                                                                                                                          |                                     |                       | 4                                                                                                                                 | 0% (0-1)                                                                    | 70% (46-86)              | 96% (91-99)              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                     |                                                                                                                          |                                     |                       | 8                                                                                                                                 | 18% (5-50)                                                                  | 95% (80-99)              | 100% (98-100)            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                     |                                                                                                                          |                                     |                       | ≥16                                                                                                                               | 100% (15-100)                                                               | 100% (93-100)            | 100% (99-100)            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                     | 1.0-3.0 **                                                                                                               | LR 63.13                            | 5-10                  | ≤1                                                                                                                                | 0% (0-2)                                                                    | 0% (0-65)                | 0% (0-95)                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                     |                                                                                                                          |                                     |                       | 2                                                                                                                                 | 4% (1-22)                                                                   | 76% (30-96)              | 97% (82-100)             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                     |                                                                                                                          |                                     |                       | 4                                                                                                                                 | 35% (17-59)                                                                 | 98% (94-99)              | 100% (99-100)            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                     |                                                                                                                          |                                     |                       | 8                                                                                                                                 | 80% (47-95)                                                                 | 100% (99-100)            | 100%                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                     |                                                                                                                          |                                     |                       | ≥16                                                                                                                               | 100% (75-100)                                                               | 100%                     | 100%                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                                                                                     | >3.0 **                                                                                                                  | LR ∞                                |                       | --                                                                                                                                | 100% (4-100) ††                                                             | 100% (79-100)            | 100% (98-100)            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |



# Machine-learning algorithms

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## Strengths of human & artificial intelligence

### Human intelligence



- Creative thinking
- Highly adaptable
- Flexible in new situations
- Emotional intelligence
- Has common sense

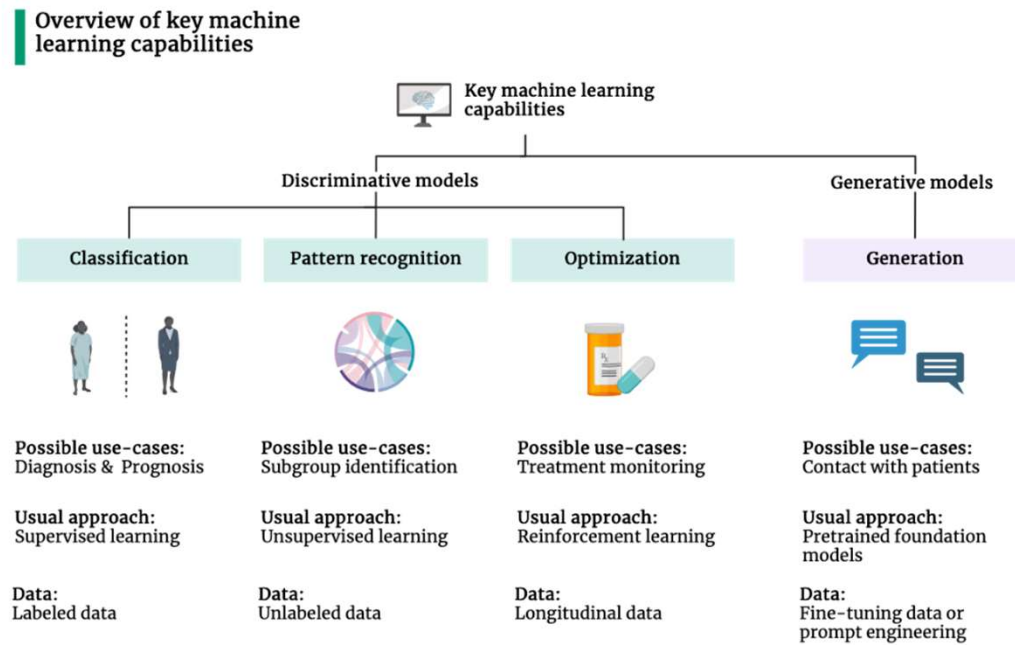
### Artificial intelligence



- High dimensional data
- Consistent and accurate
- Can deal well with probabilities
- Does not tire

*Submitted*

# Machine-learning algorithms in diagnostics

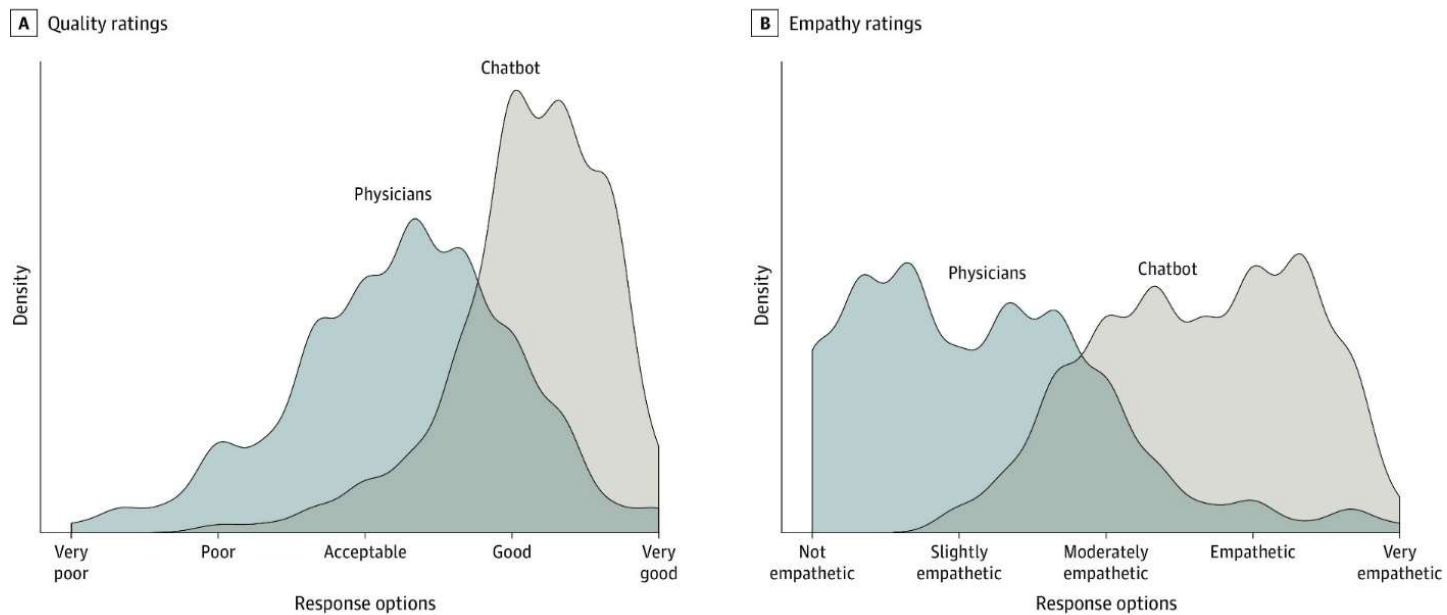


Created with biorender.com

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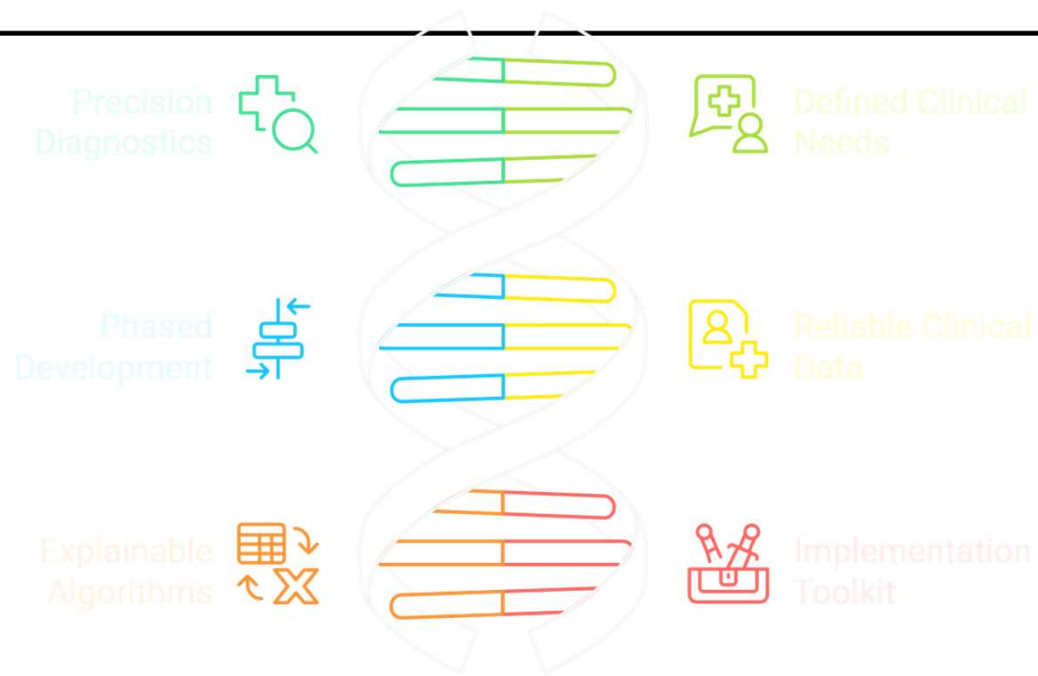
## AI vs. physicians' telemedicine services

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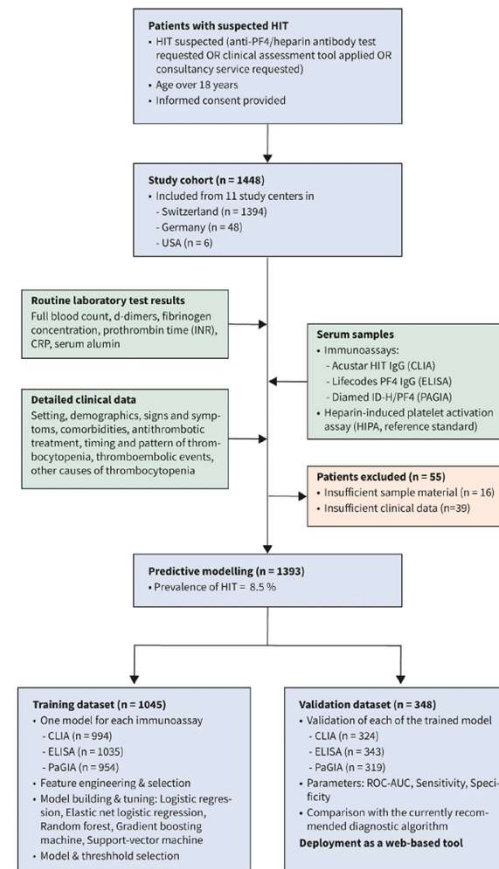
JAMA Intern Med. 2023 Jun; 183(6): 589–596.

# Essentials of Diagnostic Innovation



# A machine-learning model for reducing misdiagnosis in heparin-induced thrombocytopenia: A prospective, multicenter, observational study

Henning Nilius,<sup>a</sup> Adam Cuker,<sup>b</sup> Sigve Haug,<sup>c,d</sup> Christos Nakas,<sup>e,f</sup> Jan-Dirk Studt,<sup>g</sup> Dimitrios A. Tsakiris,<sup>h</sup> Andreas Greinacher,<sup>i</sup> Adriana Mendez,<sup>j</sup> Adrian Schmidt,<sup>k</sup> Walter A. Willemin,<sup>l</sup> Bernhard Gerber,<sup>m</sup> Johanna A. Kremer Hovinga,<sup>n</sup> Prakash Vishnu,<sup>o</sup> Lukas Graf,<sup>p</sup> Alexander Kashev,<sup>q</sup> Raphael Sanitman,<sup>r</sup> Tamam Bakchoul,<sup>s</sup> and Michael Nagler<sup>a,\*</sup>



# The TORADI-HIT algorithm



INTENDED USE

ALGORITHM

EVIDENCE

PERFORMANCE

LIMITATIONS

LEGAL NOTICE

The TORADI-HIT algorithm is a validated diagnostic instrument to calculate the probability of HIT in individual patients.

Platelet count (nadir) [ $10^9/L$ ]

72

CRP (C-reactive protein; if available) [mg/L]

12

Type of immunoassay

Acustar HIT-IgG (CLIA) [U/mL]

Numeric immunoassay test result

1

For the Diamed ID-H/PF4 use Titer<sup>-1</sup>. E.g. use 64 instead of 1:64

Did the patient receive unfractionated heparin during the current hospital stay?

Yes

Timing of the thrombocytopenia

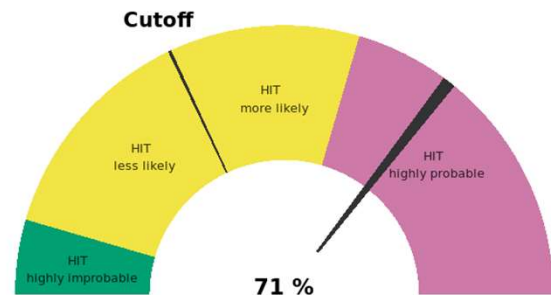
Day 5-10, or day 1 if recent heparin exposure

Other causes of thrombocytopenia

No other cause apparent

Calculate probability

Results



Cutoff

71 %

Interpretation

The classification probability of HIT is 71 %. The probability of HIT is very high with values in the red area (90% of HIT-positive patients have values in the red area).



## Conclusions - Diagnosis

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- The results of diagnostic tests influence practically all medical decisions.
- The performance of diagnostic tests in clinical practice is much worse than assumed
- This can be improved with stringently designed clinical studies
- New tools (ML/AI, etc) that integrate more diagnostic information have great potential to improve patient care and processes (costs!)

CLINICAL GUIDELINES

Check for updates

## American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia

Adam Cuker,<sup>1,2</sup> Gowthami M. Arepally,<sup>3</sup> Beng H. Chong,<sup>4</sup> Douglas B. Cines,<sup>1,2</sup> Andreas Greinacher,<sup>5</sup> Yves Gruel,<sup>6</sup> Lori A. Linkins,<sup>7</sup> Stephen B. Rodner,<sup>8</sup> Sixten Selleng,<sup>9</sup> Theodore E. Warkentin,<sup>7,10</sup> Ashleigh Wex,<sup>11</sup> Reem A. Mustafa,<sup>12,13</sup> Rebecca L. Morgan,<sup>12</sup> and Nancy Santesso<sup>12</sup>

SYSTEMATIC REVIEW

Check for updates

## Management of heparin-induced thrombocytopenia: systematic reviews and meta-analyses

Rebecca L. Morgan,<sup>1</sup> Vahid Ashoorian,<sup>2</sup> Adam Cuker,<sup>3,4</sup> Houshe Begum,<sup>1</sup> Stephanie Ross,<sup>1</sup> Nina Martinez,<sup>5</sup> Beng H. Chong,<sup>6</sup> Lori A. Linkins,<sup>7</sup> Theodore E. Warkentin,<sup>7,8</sup> Wojtek Wiercioch,<sup>1,9</sup> Robby Nieuwlaat,<sup>1,9</sup> Holger Schünemann,<sup>1,7,9</sup> and Nancy Santesso<sup>1,9</sup>

<sup>1</sup>Department of Health Research Methods, Evidence and Impact, and <sup>2</sup>Michael G. DeGroote Centre for Medicinal Cannabis Research, McMaster University, Hamilton, ON, Canada; <sup>3</sup>Department of Medicine and <sup>4</sup>Department of Pathology & Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; <sup>5</sup>Independent Researcher, Atlanta, GA; <sup>6</sup>Department of Haematology, University of New South Wales, Sydney, NSW, Australia; and <sup>7</sup>Department of Medicine, <sup>8</sup>Department of Pathology and Molecular Medicine, and <sup>9</sup>Michael G. DeGroote Cochrane Canada Centre, McMaster University, Hamilton, ON, Canada

*«We found primarily noncomparative studies and case series assessing effects of treatments, which led to low to very low certainty evidence.»*

Theme Issue Article

## Management of the multiple phases of heparin-induced thrombocytopenia

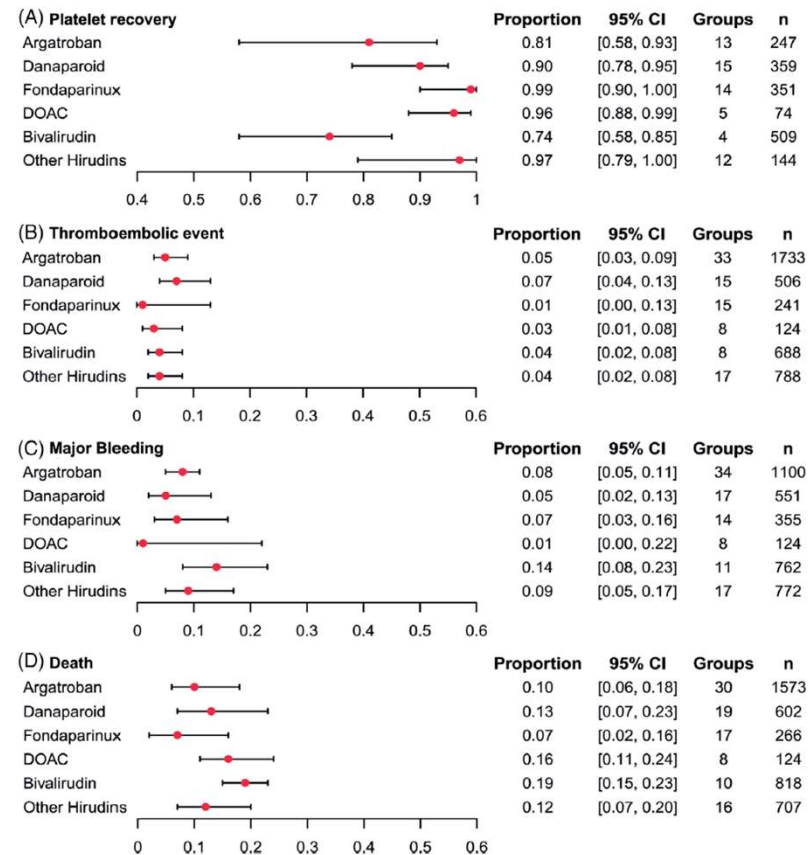
Adam Cuker

Department of Medicine and Department of Pathology & Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

|                  | Suspected HIT | Acute HIT | Subacute HIT A | Subacute HIT B | Remote HIT |
|------------------|---------------|-----------|----------------|----------------|------------|
| Platelet count   | Decreased     | Decreased | Normal         | Normal         | Normal     |
| Thrombotic risk  | ?             | Increased | Increased?     | Increased?     | Normal     |
| Functional assay | ?             | +         | +              | -              | -          |
| Immunoassay      | ?             | +         | +              | +              | -          |

Table 1: The multiple phases of HIT.

<http://dx.doi.org/10.1160/TH16-02-0084>  
*Thromb Haemost* 2016; 116: 835–842



*Am J Hematol.* 2021;1–11.

# Acknowledgements

## Inselspital Bern

Henning Nilius, J. Kremer Hovinga, M. Horn, C. Nakas, M. Masoodi, A. Eggel, R. Boss, A. Burger, S. Naas, T. Sauter, C. Largiadèr, M. Massodi, T. Fröhlich, P. Jent, G. Erdös, U. Amstutz, M. Fiedler

## Switzerland

R. Snitman, J. Hastings, S. Haug, J.D. Studt, W.A. Wullemin, L. Alberio, B. Gerber, A. Schmidt, D. Tsakiris, A. Mendez, P. Fontana, L. Alberio, L. Graf, A. Hammerer-Lercher

## International project partners

A. Cuker, T. Bakchoul, A. Greinacher, A. Koster, I. Birschmann, F. Cognasse, J.P. Goetze

$u^b$

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## Our Applications

### TORADI-HIT

TORADI-HIT is a user-friendly machine learning algorithm that integrates clinical and laboratory data to diagnose heparin-induced thrombocytopenia (HIT). It outperforms current diagnostic methods and has been externally validated. The algorithm is designed to support fast and reliable decision-making—especially when time is critical.

[TORADI-HIT App](#) 

### MBD-Check

MBD-Check is an interpretable machine learning decision support tool for the preoperative screening of mild bleeding disorders. It is designed to simplify healthcare processes by reducing unnecessary referrals and improving patient care. The tool has demonstrated high diagnostic accuracy and was rated as user-friendly by clinicians.

[MBD-Check App](#) 

<https://pfam.ch>

