Multimedia Appendix 2. Evaluation of hypotheses to overcome the challenge of variability among patients in cardiotoxicity research.

Hypotheses	Novelty	Keywords	Publications (n=18), n (%)	Evaluator 1[a] score	Evaluator 2[b] score	Evaluator 3[c] score	Group consensus score
1. Integrating patient-specific genetic profiles with AI[d] algorithms can predict individual susceptibility to cardiotoxicity, enabling personalized treatment plans	High	"genetic profiles," "AI," "cardiotoxicity," "personalized treatment"	0 (0)	4	4	4	4
2. Using patient-derived cardiomyocytes from diverse genetic backgrounds in high-throughput screening can identify genetic variants associated with increased cardiotoxicity risk	High	"patient-derived cardiomyocytes," "genetic backgrounds," "high-throughput screening," "cardiotoxicity risk"	0 (0)	3	3	4	3

3. Longitudinal studies using wearable health monitors can capture real-time cardiac data, helping to identify patient-specific patterns and early signs of cardiotoxicity	Moderate	"wearable health monitors," "real-time cardiac data," "cardiotoxicity patterns"	0 (0)	4	4	4	4
4. Epigenetic profiling of patients before and after drug administration can reveal markers that predict susceptibility to cardiotoxic effects	High	"epigenetic profiling," "drug administration," "cardiotoxicity markers"	0 (0)	4	4	4	4
5. Applying machine learning to electronic health records can uncover hidden correlations between patient demographics, comorbidities, and cardiotoxicity risk	Moderate	"machine learning," "electronic health records, EHRs," "patient demographics," "comorbidities," "cardiotoxicity risk"	0 (0)	4	5	3	4
6. Developing a multi-omics approach that combines genomics, proteomics, and	High	"multi-omics," "genomics,"	0 (0)	5	5	4	5

metabolomics can provide a comprehensive understanding of individual variability in cardiotoxic responses		"proteomics," "metabolomics," "cardiotoxicity variability"					
7. Using CRISPR[e] technology to create patient-specific iPSC[f]-derived cardiomyocytes can help study the impact of individual genetic differences on cardiotoxicity	High	"CRISPR," "iPSC-derived cardiomyocytes," "genetic differences," "cardiotoxicity"	2 (11)	4	4	3	4
8. Investigating the role of microbiome diversity in cardiotoxicity can reveal how gut microbiota influence individual susceptibility to cardiac damage from drugs	High	"microbiome diversity," "cardiotoxicity," "gut microbiota," "cardiac damage"	1 (6)	4	4	4	4
9. Pharmacogenomics studies can identify specific gene-drug interactions that contribute to variability in cardiotoxic responses among patients	Moderate	"pharmacogenomics," "gene-drug interactions," "cardiotoxicity	0 (0)	4	4	3	4

		variability”					
10. Utilizing advanced imaging techniques, such as cardiac MRI[g], can non-invasively assess patient-specific cardiac changes and predict cardiotoxicity risk	Moderate	“advanced imaging,” “cardiac MRI,” “patient-specific cardiac changes,” “cardiotoxicity risk”	0 (0)	4	4	3	4
11. Exploring the impact of hormonal differences, such as variations in sex hormones, on cardiotoxicity can help understand gender-specific risks	Moderate	“hormonal differences,” “sex hormones,” “cardiotoxicity,” “gender-specific risks”	0 (0)	4	4	3	4
12. Conducting large-scale genome-wide association studies can identify common genetic variants that increase the risk of cardiotoxicity	Moderate	“genome-wide association studies, GWAS,” “genetic variants,” “cardiotoxicity risk”	15 (83)	5	3	3	3

13. Studying the interaction between environmental factors, such as diet and lifestyle, and genetic predisposition can provide insights into patient-specific cardiotoxicity risk	Moderate	“environmental factors,” “diet,” “lifestyle,” “genetic predisposition,” “cardiotoxicity”	0 (0)	4	4	4	4
14. Investigating the role of immune system variability in cardiotoxicity can reveal how individual differences in immune response contribute to cardiac damage	Moderate	“immune system variability,” “cardiotoxicity,” “immune response,” “cardiac damage”	0 (0)	5	5	3	4
15. Applying personalized medicine approaches to adjust drug dosages based on individual metabolic profiles can reduce the risk of cardiotoxicity	Moderate	“personalized medicine,” “drug dosages,” “metabolic profiles,” “cardiotoxicity”	0 (0)	5	5	4	5

16. Developing predictive biomarkers from blood-based assays can provide non-invasive tools for assessing individual cardiotoxicity risk before drug administration	High	“predictive biomarkers,” “blood-based assays,” “cardiotoxicity risk,” “non-invasive tools”	0 (0)	5	5	3	5
17. Analyzing patient-specific variations in drug metabolism enzymes can help predict and mitigate cardiotoxicity risk	Modera te	“drug metabolism enzymes,” “patient-specific variations,” “cardiotoxicity risk”	0 (0)	4	4	4	4
18. Using virtual clinical trials with simulated patient populations can model and predict variability in cardiotoxic responses across diverse demographics	High	“virtual clinical trials,” “simulated patient populations,” “cardiotoxicity variability”	0 (0)	4	4	3	4

19. Investigating the impact of epitranscriptomic modifications, such as RNA methylation, on cardiotoxicity can uncover new layers of individual variability in drug response	High	“epitranscriptomic modifications,” “RNA methylation,” “cardiotoxicity,” “drug response”	0 (0)	4	4	4	4
20. Implementing AI-driven predictive analytics on patient genomic data can enhance the identification of at-risk individuals and tailor cardioprotective strategies accordingly	High	“AI-driven predictive analytics,” “genomic data,” “cardiotoxicity,” “cardioprotective strategies”	0 (0)	4	4	4	4

[a]Author YL (MD and PhD, professor).

[b]Author TG (MD, final-year PhD candidate).

[c]Author CY (MD, first-year PhD student).

[d]AI: artificial intelligence.

[e]CRiSPR: clustered regularly interspaced short palindromic repeats.

[f]iPSC: induced pluripotent stem cell.

[g]MRI: magnetic resonance imaging.