European Network of Expertise (NoE) on Omics

(Joint Action JANE-2 – GA 101183265 – WP9)

Strengthening Joint Clinical Assessments for Omics-based Technologies by

Addressing Regulatory gaps in the Draft Implementing Regulation under Health Technology Assessment (HTA) Regulation 2021/2282

June 2025

Key Issues and Recommendations

What is JANE-2?

JANE-2 is an ambitious initiative, stemming from Europe's Beating Cancer Plan, with the aim to implement seven new European Networks of Expertise in cancer, addressing: 1) complex and poor prognosis cancers; 2) palliative care; 3) survivorship; 4) personalized primary and secondary prevention; 5) omics technologies, 6) hi-tech medical resources; and 7) adolescents and young adults with cancer. It represents 121 partners across 29 European countries.

Why a Network of Expertise on Omics Technologies?

Omics technologies are revolutionizing the management of patients with cancers, haematological malignancies, as well as rare diseases. These innovative tools go beyond supporting precision diagnosis and treatment. They also improve cancer prediction, early detection, and disease monitoring. Genomics and transcriptomics are currently the most widely used in clinical practice. However, emerging fields such as epigenomics, proteomics, and metabolomics, as well as multi-omics integration, including AI tools, are rapidly advancing and poised to play a significant role in the future.

The ambition of the Network of Expertise (NoE) on Omics is to support the integration of innovative omics technologies into the standard of care at the different steps of cancer management in a sound and sustainable manner, achieving equitable access to these services for all EU citizens.

Strengthening Joint Clinical Assessments for Omics Technologies: addressing regulatory gaps in the EU HTA Implementing Regulation

The JANE 2 NoE on Omics Technologies welcomes the opportunity to contribute to the public consultation on the draft **Joint Clinical Assessments** Implementing Regulation of the EU Health Technology Assessment (HTA) Regulation 2021/2282 and to provide a detailed analysis of the topic, as well as recommendations from a European consortium of experts.

To ensure that innovative medical technologies, including omics-based ones, can reach patients efficiently and safely, it is essential that the regulatory frameworks—namely the Medical Device Regulation (MDR), the *In Vitro* Diagnostic Regulation (IVDR) and the HTA Regulation—are streamlined, aligned, and implemented in a coherent and complementary manner. These laws serve distinct but interdependent purposes:

- MDR and IVDR ensure that devices meet high standards for safety and performance,
- while the HTA Regulation assesses their clinical value and cost-effectiveness for health system adoption.

If these frameworks operate in silos—each demanding overlapping, time-consuming, and often marginally beneficial evidence—Europe risks undermining its own innovation ecosystem. The consequences are not just bureaucratic inefficiencies: they translate into delayed patient access to life-saving technologies, inflated development and compliance costs, and a wasteful duplication of effort across regulatory and HTA systems. Such fragmentation slows down medical progress, drains public resources, and ultimately fails the patients these frameworks are meant to serve. Therefore, **legal and procedural alignment is crucial**—not only to **reduce administrative burden** and **promote innovation**, but also to **ensure that the CE-marked technologies evaluated under MDR and IVDR can seamlessly transition into HTA processes without unnecessary delays**. This requires coordinated evidence planning, reciprocal recognition of assessments where appropriate, and a clear, interoperable interface between regulatory and HTA bodies. Such integration would fulfill the shared objectives of these regulations: to protect patients, support informed health system decisions, and enable equitable access to effective and efficient medical innovations across the EU.

While the HTA Regulation offers a pathway to strengthen coordinated clinical assessments for high-risk devices and 'diagnostics', omics-based technologies, including but not restricted to whole-genome sequencing (WGS), multi-omics platforms, and AI-driven algorithms, pose distinct methodological and regulatory challenges that are not sufficiently accounted for in the current draft. Drawing from *ad hoc* expertise as well as real-world (RW) implementation experience of the JANE-2 NoE on Omics partners, this position paper outlines key structural concerns and provides concrete recommendations for the way forward.

KEY ISSUE 1: Incompatibility of dossier templates with Real-World Omics Evidence

Article 9(2); Annexes I–II (HTA dossier template for IVDs and medical devices)

The current draft proposal for Implementing Regulation mandates the use of structured dossier templates (Annexes I–V), modelled primarily on the pharmaceutical evaluation paradigm. These templates emphasize standardized evidence hierarchies rooted in randomized controlled trials (RCTs), tabular presentation of treatment effects, and fixed PICO (Population–Intervention–Comparator–Outcome) parameters. While this structure is long established in medicinal product evaluation, it is incompatible with the evidence ecosystems that support omics-based technologies.

Omics evidence, whether derived from the analyses of genome, transcriptome, proteome, metabolome, or other biological molecules, whether considering multiple omics layers and/or including AI tools (in the near future), is typically built on:

- Retrospective biobank-linked cohort studies using large-scale sequencing and clinical annotation
- RW evidence from national registries, integrated hospital records, or multi-center networks
- *In silico* validation via computational simulations, including bootstrap resampling, cross-validation, or unsupervised learning
- Adaptive or machine learning models that evolve based on new data inputs, which challenge static trial designs

The dossier templates, as currently proposed, do not provide dedicated sections for presenting these data types. As a result, HTA developers must either retrofit non-standard data into RCT-style tables—

introducing artificial distortions—or rely on extensive narrative appendices that risk being discounted as "non-comparable." Additionally, formatting constraints across Annexes I–V create a steep compliance burden, particularly for SMEs, academic developers, and hospital-based innovation units, who may lack dedicated regulatory support and formatting expertise.

Consequences:

- Omics dossiers structured around RW cohorts or computational models may be downgraded due to a lack of formal trial design, even when clinical utility is demonstrated. This **undermines both scientific validity and innovation potential**.
- Misaligned dossier formats increase the risk of HTA bodies issuing clarification requests, **delaying JCAs, and exhausting limited submission windows**.
- Meeting the highly granular, table-driven formatting expectations will often require external regulatory consultants, especially for non-industry stakeholders. This introduces **significant costs and resource drain,** estimated at 20–40% of total dossier preparation effort for omics-based developers.
- Developers may delay submission of promising omics tools due to the inability to capture non-RCT validation data in accepted templates, **slowing down patient access and stalling reimbursement pathways**.

Recommendation 1: *To address these structural mismatches, we recommend the implementation of modular dossier templates that:*

1. *Allow for integration of structured RW evidence, with dedicated sections for cohort design, data quality metrics, and confounder control strategies*
2. *Include narrative components supported by graphical outputs (e.g., ROC curves, calibration plots, decision curves) that contextualize evidence from machine learning models or digital biomarkers*
3. *Provide validation tiering models (e.g., analytical → clinical performance → utility), enabling progressive evidence development across different technology readiness levels*
4. *Accept in silico simulations and external validation where patient-level data sharing is restricted (e.g., for rare disease applications)*

This modular approach is in line with emerging practice in complex diagnostics assessment.

KEY ISSUE 2: Overreliance on Centralized HTA IT Platform

Article 20, Annex V (submission mechanisms and communications)

The current draft proposal for the Implementing Regulation establishes the HTA IT platform (Article 20) as the sole channel for submission, interaction, and publication throughout the Joint Clinical Assessment process. While a centralized platform is essential for harmonization, the current proposal lacks critical operational, technical, and governance details. This includes omissions related to user access protocols, digital infrastructure capacity, acceptable file formats and sizes, service-level guarantees, and cybersecurity safeguards.

These gaps are especially problematic for omics-based technologies, which routinely involve the transmission of large and complex files at the different steps of the bioinformatics pipeline (e.g., BAM, FASTQ, VCF), and machine learning model scripts. Moreover, omics evidence generation is increasingly dynamic and may require frequent updates or version tracking. Without scalable infrastructure, redundancy mechanisms, and technical transparency, the platform could act as a single point of failure in the regulatory process.

The risk is particularly critical for decentralized and public institutions, such as regional hospitals, clinical laboratories, and university-based Health Technology Developers, which may lack in-house IT teams or the bandwidth to manage large submissions under rigid, undocumented constraints. Without tailored support and clear data protection frameworks, these stakeholders may face technical or legal barriers to full participation in EU-level HTA.

Consequences:

- In the absence of documented limits or technical guidelines, **Health Technology Developers (HTD) may experience failed uploads or file rejections**, especially for genomic datasets exceeding several gigabytes.
- Large or multi-part datasets lacking version control, checksum verification, or submission traceability could result in **unverified uploads or compliance risks for assessors**.
- Without platform redundancy or fallback channels, even brief outages could stall assessments. The absence of a defined service-level agreement (SLA) **undermines continuity for all users**.
- Assessors may be unable to access necessary files due to format incompatibilities or platform lags, **delaying both scoping and evaluation milestones**.
- The lack of user support and infrastructure parity creates structural inequities. Smaller entities may be effectively excluded from participation in JCAs, **contradicting principles of inclusiveness and innovation support**.
- With no clearly disclosed data protection and data privacy-aligned measures, such as encryption standards, anonymization protocols, or audit logging, **the platform may expose patient-level genomic data to legal and reputational risks**.

Recommendation 2*: To ensure that the HTA IT platform supports both efficiency and equity in the JCA process, particularly for omics technologies, the following four measures are strongly recommended:*

1. *Establish secure, high-throughput data transfer alternatives—such as encrypted FTP portals, SFTP servers, or approved cloud storage—capable of handling large bioinformatics files. Offline encrypted media submission (e.g., hard drives under chain-of-custody) should be allowed for large-volume evidence bundles, particularly from public sector developers.*
2. *The Commission should provide a comprehensive user guide that includes:*
    - *File format specifications and size limits*
    - *Bandwidth and browser requirements*
    - *Interface security features*
    - *Submission workflow diagrams*

    This guidance should be accessible in advance of the first official JCAs, to enable capacity-building and readiness.

3. *Establish a dedicated omics onboarding track, including training webinars, helpdesk support, and "sandbox" environments where HTDs can trial sample submissions and validate file compatibility. Special focus should be given to SMEs, academic developers, and clinical labs with limited regulatory infrastructure.*
4. *Ensure all data exchanged via the platform is protected by:*
    - *End-to-end encryption in transit and at rest*
    - *Access control with role-based authentication*
    - *Secure metadata handling and anonymization options*
    - *Full audit trails for file access and modification*

    Public disclosure of these safeguards will strengthen trust and encourage broader participation, especially when handling patient-level genomic data or proprietary AI models.

KEY ISSUE 3: Disruption from re-initiation clauses in Adaptive Testing Models

Articles 10(8), 19; Dossier versions V1.0.1–V1.0.5

The current draft proposal for the Implementing Regulation permits the re-initiation of Joint Clinical Assessments when new clinical evidence becomes available during the assessment process. While this aims to ensure up-to-date evaluations, it also allows for timeline extensions of up to 345 days, effectively restarting the JCA cycle. For omics-based tools, especially those incorporating machine learning or adaptive algorithms, this poses a significant challenge. These technologies often undergo frequent updates as new data improves their predictive accuracy or as they are re-trained for additional populations and indications. Consequently, developers of omics tools could face an ongoing loop of restarts, with each incremental data update triggering reassessment, thus impeding finalization and delaying patient access.

Consequences:

- Developers and investors are unable to reliably predict approval timelines, making it **difficult to align product launch, reimbursement strategy, and clinical rollout**.
- **The static JCA structure contrasts with the European Medicines Agency's adaptive evaluation** model, which allows staged evidence submission without restarting the regulatory timeline.
- Omics technologies often depend on iterative improvements, such as periodic AI recalibration or the inclusion of emerging biomarkers. **A rigid re-initiation approach penalizes this innovation model**.

Recommendation 3: *To support both scientific rigor and regulatory agility, the regulation should adopt a rolling, module-based submission system. Specifically, fixed checkpoints within the assessment period should allow developers to submit supplementary clinical or analytical data without triggering a full reset of the JCA timeline. This would mirror the EMA's rolling review process and builds on pilot practices from EUnetHTA and the HTx Horizon 2020 project. Such a system would maintain assessment continuity, reduce delays, and better accommodate the dynamic nature of omics-based diagnostics.*

KEY ISSUE 4: Lack of clear role for Clinical Centers in Expert identification

Articles 3(7)(d), 8, 9(3); no dedicated annex on omics

The draft implementing regulation (Article 8) introduces important criteria for selecting individual experts for Joint Clinical Assessments (JCAs), prioritizing those with cross-national expertise. However, it does not sufficiently define the mechanisms by which clinical centers, academic hospitals, or translational research institutions can nominate or recommend domain-relevant experts. This omission is significant, as clinical centers, particularly university hospitals and regional cancer institutes, hold deep, practice-based knowledge across multiple therapeutic areas and have direct experience with the implementation of omics-based technologies.

These institutions are often at the forefront of clinical validation, cohort data generation, and RW evidence studies. Their investigators are uniquely positioned to offer insights into the clinical utility, workflow integration, and patient impact of complex omics platforms. Without a structured process for their involvement in expert selection, the regulation risks excluding some of the most qualified stakeholders from JCA evaluations.

Consequences:

- Experts nominated exclusively through existing EU networks or administrative channels **may lack firsthand implementation experience**, particularly in fast-evolving fields like omics technologies.
- Smaller or newer institutions, particularly from underrepresented Member States, **may be excluded if nomination is informally driven or lacks transparency**, reducing diversity in expert perspectives.
- Omics technologies are highly context-sensitive. Without representation from practicing clinicians and investigators familiar with implementation challenges, assessments **may overlook usability, workflow compatibility, or population-level considerations**.

Recommendation 4: *To ensure that JCAs benefit from robust, context-rich expertise, we recommend that the Implementing Regulation define a formal mechanism for expert identification that includes academic hospitals and clinical centers as nominating bodies. This process should:*

1. *Be transparent and regulated, with clear criteria for eligibility and documentation of relevant clinical or translational experience.*
2. *Include provisions for direct invitations or calls for expression of interest distributed via national HTA focal points or recognized health networks (e.g., EUnetCCC, other NoEs, ERNs, national cancer networks, etc.).*[1]
3. *Allow for periodic review and renewal of the expert database to include emerging expertise, particularly from fast-moving domains such as omics-based stratification tools and digital biomarkers.*

[1] *Casali PG, Antoine-Poirel H, Berrocoso S, Blay JY, Dubois T, Ferrari A, Fullaondo A, Hovig E, Jagodzińska-Mucha P, Ługowska I, Kaasa S, Nicoară D, Pletsa V, Provenzano S, Santoro M, Šekerija M, Van Hoof W, Vyas M, Trama A; JANE Consortium.* ***Health networking on cancer in the European Union: a 'green paper' by the EU Joint Action on Networks of Expertise (JANE). ESMO Open****. 2025 Feb;10(2):104126. doi: 10.1016/j.esmoop.2024.104126. Epub 2025 Jan 27. PMID: 39874899 (https://pmc.ncbi.nlm.nih.gov/articles/PMC11799966/)*

Such a process would improve the scientific rigor and clinical relevance of JCAs while it will also strengthening stakeholder trust, inclusiveness, and equitable participation across the EU.

KEY ISSUE 5: Procedural Timelines are misaligned with the complexity of Omics-Based Technologies

Articles 3(2), 4(2), 8, 10, 11; Annex I (dossier template and procedural history)

The current draft regulation outlines narrowly defined and rigid procedural timelines for key milestones within the Joint Clinical Assessment process. These include a 5-day window for notified bodies to submit CE-certification documents and a 100-day deadline for HTDs to prepare and submit their full clinical dossier. While such timeframes may be manageable for conventional, single-analyte devices with stable data packages, they are not compatible with the operational realities of omics-based technologies.

Omics technologies depend on complex, multi-layered evidence generation. These processes typically involve iterative validation across multiple cohorts, integration of retrospective/prospective data, alignment with evolving standards for analytical and clinical validity, clinical utility, and, increasingly, dynamic algorithm updates. For example, AI-augmented tools often require post-CE recalibration using RW performance data. This iterative nature makes the construction of a static and finalized submission dossier within 100 days highly unrealistic.

Moreover, HTDs affiliated with public institutions, including academic hospitals, universities, and public–private consortia, face additional structural barriers. These include internal governance procedures, institutional review board approvals, and limitations on rapid mobilization of multidisciplinary resources. These constraints make it nearly impossible for public developers to comply with the prescribed deadlines, placing them at a systemic disadvantage compared to larger industrial actors with dedicated regulatory infrastructure.

Consequences:

- Developers may require additional time to finalize analytical and clinical performance metrics, complete ongoing validation studies, or reconcile data from real-world registries and randomized clinical trials. Rushing this process can **compromise data quality and completeness**.
- Tight deadlines heighten the likelihood of **incomplete or substandard dossiers**, which may trigger re-initiation of assessments or regulatory rejection. This risk is particularly acute for omics tools, where datasets are large, heterogeneous, and often distributed across institutions.
- The procedural burden, when combined with unrealistic deadlines, deters innovative non-commercial developers. This **risks limiting the diversity of submissions** and slowing the development of testing solutions in the different areas of precision cancer medicine, including rare cancers as well as cancers in the young population.

Recommendation 5. *To ensure fairness, scientific adequacy, and technology developer readiness, we recommend that the Implementing Regulation adopt differentiated procedural windows that account for the complexity of the technology being assessed. Specifically:*

1. *Extend the deadline from 5 days to at least 10 working days for the submission of key documents and data (ref. Articles 3(2) and 4(2)).*

2. *Extend the dossier preparation period for omics-based technologies to at least 150 days (instead of 100) from the confirmation of the scoping agreement.*

Differentiated timelines would not only improve compliance and evidence quality but would also help ensure equitable access for academic and public-sector innovators to EU-level assessment mechanisms.

KEY ISSUE 6: Lack of feedback and Transparency toward clinical data Contributors

Article 21 – Confidentiality Requests

Article 21 of the draft Implementing Regulation outlines the process for handling confidentiality in the publication of Joint Clinical Assessment reports. While the article details the obligations of the Commission to consult with the HTD regarding the publication or redaction of potentially sensitive content, it fails to include provisions for feedback to or acknowledgment of clinical centers or investigators who contribute critical data to the assessment process.

Omics-based technologies often depend on RW data sourced from hospital-based studies, biobank-linked cohorts, and regional or academic clinical centers. These institutions are instrumental in generating clinical performance evidence, particularly when randomized trials are infeasible. However, under the current draft, there is no requirement for the Commission or the JCA Subgroup to notify these contributing centers when their input is published, redacted, or deemed confidential. Nor is there any transparency mechanism that allows contributing institutions to verify how their data has been represented, or omitted, in the final public report.

This omission not only risks undermining the collaborative ethos of EU-wide JCAs but also limits the ability of data contributors to understand and learn from how their evidence is used, potentially eroding trust and reducing future engagement in EU-level assessments.

Consequences:

- Without notification or review access, **clinical investigators may not recognize** whether their input has been misrepresented, de-emphasized, or excluded from the final report.
- When contributions are anonymized or redacted without feedback, **institutions may perceive JCAs as extractive rather than collaborative**, especially in cases where no acknowledgment or reciprocal access is provided.
- Clinical centers often rely on acknowledgment in regulatory and HTA publications to **justify the use of institutional resources for research**. The inability to confirm how and where their data has been incorporated **weakens this pathway**.
- Decisions on redaction made solely between the HTD and the Commission, without consultation with data originators, may result in **unnecessary or inappropriate concealment of scientifically relevant content**.

Recommendation 6: *To address these transparency and recognition gaps, we recommend the inclusion of the following provisions in Article 21 or associated guidance documents:*

1. *When evidence from identifiable hospital-based investigators has been included in the JCA report (either public or redacted), those contributors should be notified at the point of publication or redaction.*
2. *Where feasible, health (patient) data contributors should be given a limited opportunity (e.g., 10 working days) to verify how their data has been characterized in non-confidential summaries. This would ensure factual accuracy and build trust.*
3. *Final JCA reports should include non-commercial, non-promotional acknowledgments of institutions that contributed to the evidence base, in line with scientific best practice and informed consent principles for secondary use of data.*
4. *If clinical performance data generated by third-party institutions is excluded or redacted at the request of the HTD, the Commission should assess whether such redaction is proportionate and whether it prevents public understanding of critical scientific information.*

KEY ISSUE 7: Fragmentation between JCA outcomes and National HTA implementation

Article 3(8), Recitals 15–17

While the Health Technology Assessment Regulation (EU) 2021/2282 introduces Joint Clinical Assessments to support a harmonized evaluation of medical devices and *in vitro* diagnostics across Member States, it stops short of requiring national HTA bodies to adopt JCA conclusions. The regulation merely states that Member States must "*give due consideration*" to JCA outcomes, without specifying how or to what extent. In practice, this has created a structural disconnect between EU-level evidence generation and national-level decision-making.

This disconnect is particularly problematic for omics-based technologies, which already face significant heterogeneity in national HTA criteria. Many Member States apply divergent standards for cost-effectiveness modeling, RW evidence acceptance, or surrogate endpoints (e.g., omics biomarkers). As a result, the intended purpose of JCAs, specifically to eliminate duplicative clinical assessments and streamline access, is not being realized.

Consequences:

- **Redundant reassessments** at the national level despite the existence of a validated EU-level JCA report.
- **Extended reimbursement delays**, particularly in countries where national processes are still heavily siloed from EU recommendations.
- **Unequal access for patients across Member States**, reinforcing existing disparities in access to advanced testing and precision cancer medicine.

This fragmentation disproportionately affects omics testing, which often involves complex, population-specific clinical pathways and relies on multi-analyte, large-scale studies and soon, AI-enhanced interpretation. Without a common evaluative framework, such technologies face repeated reassessments and risk being denied reimbursement in key markets, despite demonstrating clinical validity and clinical utility at the EU level.

Recommendation 7: *The European Commission should mandate the development of pan-European methodological guidance tailored to the evaluation of omics technologies. This guidance should include:*

1. *Standardized approaches to cost-effectiveness modeling, especially for tests that stratify treatment populations / patient groups or influence downstream care.*
2. *Value of Information (VOI) models to support early access and managed entry agreements for omics testing with evolving evidence bases.*
3. *Adaptive assessment frameworks that accommodate RW data and learning health system principles.*

This work should draw directly from ongoing EU-funded initiatives, including EUnetHTA21, HTx-Next Generation HTA projects, and outputs from the Innovative Health Initiative (IHI). A unified framework, targeted for release by 2026, would provide clarity for developers, reduce national divergences, and ensure JCAs function as a credible foundation for national HTA and reimbursement decisions. Lack of alignment threatens to render EU investments in centralized clinical assessments ineffective in improving patient access or accelerating innovation uptake.

KEY ISSUE 8: Absence of Omics Technologies-specific methodological guidance

Articles 3(7)(d), 9(3); no dedicated annex on omics

The current draft Implementing Regulation fails to provide specific methodological standards for evaluating the analytical and clinical performance of omics-based diagnostics. Unlike conventional *in vitro* diagnostic devices, omics technologies pose unique challenges in evidence generation and interpretation. These include issues such as the stability of machine learning models, generative AI tools, algorithmic bias, reproducibility across populations and datasets, and the need for mitigation of batch effects in high-throughput omics platforms.

Currently, there are no clear criteria for:

- Analytical validation of complex multiple biomarkers and/or AI-augmented tests across diverse omics data (e.g. genomics, transcriptomics, proteomics).
- Interpretability standards for AI-driven decision-support systems embedded in omics testing.
- Reproducibility thresholds for classifiers trained on high-dimensional, population-sensitive datasets.
- Acceptance of surrogate endpoints derived from molecular profiles in clinical performance evaluation.

This lack of specificity leaves HTA bodies and developers without a shared reference framework for evaluating omics tools, resulting in fragmented and inconsistent assessments across jurisdictions.

Consequences:

- **Inconsistent evaluation by HTA assessors**, leading to variable decisions across Member States, even for the same device.
- **Unclear evidentiary thresholds for market access** create uncertainty for developers and investment risks.
- **Loss of international harmonization opportunities**, especially where frameworks already established provide for omics-specific international harmonization (eg. ISO 15189)

Recommendation 8: *To address these critical gaps, the Commission should introduce a dedicated "Annex VI" focused on omics-specific evaluation methods. This annex should outline:*

1. *Minimum performance requirements for polygenic risk scores and multi-marker tests, including validation across reference populations.*
2. *Standards for AI transparency, explainability, and bias mitigation in diagnostic algorithms.*
3. *Acceptable methods for batch effect correction and normalization across laboratories and platforms.*
4. *Cross-validation protocols and generalizability criteria for classifiers used in clinical decision support.*

This annex should build on existing methodological work from:

1. *EUnetHTA Joint Action 3 and EUnetHTA21 pilot assessments,*
2. *EMA reflection papers on AI in medicines and diagnostics,*
3. *Relevant ISO standards such as ISO 15189 (medical laboratories), ISO 13485 (quality management), and ISO/TS 20428 (structured omics data).*

CONCLUDING REMARKS

The JANE 2 Network of Expertise on Omics Technologies, established under Europe's Beating Cancer Plan, has reviewed the draft Implementing Regulation on Joint Clinical Assessments with the shared goal of improving equitable access to innovative omics diagnostics across Europe. As our position paper demonstrates, the current draft, while a critical step forward, requires urgent refinements to fully accommodate the unique scientific, operational, and regulatory characteristics of omics-based technologies.

Omics-based testing is transforming the way we detect, stratify, and manage patients with cancer (as well as rare diseases), yet it challenges conventional HTA models with their complexity, adaptive nature, and dependence on RW data. Unless addressed, the current structural and procedural gaps in the draft regulation will undermine the promise of JCAs, delay patient access, penalize public-sector innovators, and jeopardize EU leadership in precision health.

This is a pivotal opportunity for the European Commission and the HTA Coordination Group to ensure that the HTA Regulation, the Medical Device Regulation, and the *In Vitro* Diagnostic Regulation work in synchrony—not in silos—towards a coherent and aligned implementation that delivers a safe, effective, and high-value healthcare system to patients without unnecessary delay, duplication, or disparity across Member States.

We urge the European Commission to incorporate the following eight key recommendations, prioritized according to the JANE 2 Network of Expertise on Omics Technologies, into the final Implementing Regulation and related guidance documents.

Recommendation 1: Adopt modular submission dossier templates that reflect RW omics data, machine learning models, and staged validation.

Recommendation 2: Ensure the HTA IT platform supports large data, secure transfer, and equal access for public and SME developers.

Recommendation 3: Introduce a rolling submission model to prevent delays from reassessment and support adaptive omics diagnostics.

Recommendation 4: Allow the healthcare system to nominate experts and strengthen JCA relevance and inclusivity.

Recommendation 5: Extend submission deadlines and dossier timelines to reflect the complexity of omics technologies.

Recommendation 6: Recognize and inform clinical contributors whose data support JCAs, ensuring transparency and trust.

Recommendation 7: Develop unified EU guidance for omics-specific HTA, covering cost-effectiveness, RW data, and adaptive models.

Recommendation 8: Create an Annex VI with dedicated evaluation standards for omics technologies, including, among others, innovative omics, multi-omics, AI tools, and cross-validation.

To ensure JCAs fulfill their potential, the final implementing act must aim for the right balance—**embedding flexibility**, **clear methodology**, and **adaptable regulation**. This will ensure timely, fair, and innovation-friendly access to top-quality omics-driven technologies across the EU.

The JANE-2 NoE on Omics consortium stands ready to collaborate with the Commission, the Member State Coordination Group, and other stakeholders in shaping annexes, templates, and capacity-building programs essential for HTA readiness.

We call for an inclusive, iterative implementation strategy that builds in pilot evaluations and RW testing of JCA methods for the omics used to manage patients with cancers (e.g., single omics, multi-omics, support of AI-technology, etc).

Only with such reforms can the HTA framework truly support innovation, protect patient safety, and ensure that all EU citizens benefit from the next generation of precision cancer medicine.

On behalf of the NoE on Omics in Cancer,

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Key Message:

JANE-2 brings together 121 institutions in 29 countries to power Europe's Beating Cancer Plan. The mission: fast-track omics into cancer care—fair, fast, and future-proof. These high-impact tools evolve fast and need a legal framework that keeps up.

The draft HTA regulation falls short on eight fronts: it ignores real-world omics data, lacks IT capacity, punishes adaptive tools, shuts out clinical expertise, rushes timelines, overlooks data contributors, offers no shared guidance, and omits standards for AI-driven tools.

JANE-2 urges EU policymakers to align the regulation with real-world needs. We propose eight solutions, four require immediate action:

1. Use modular dossier templates that capture omics data, machine learning, and staged validation.
2. Equip the HTA IT platform for secure, large-scale data transfer with fair access for public and SME developers.
3. Enable rolling submissions to avoid delays and support adaptive omics-based tests.
4. Facilitate more inclusiveness for the healthcare system to nominate experts.
5. Extend submission timelines to reflect omics complexity.
6. Acknowledge clinical data contributors to foster trust and transparency.
7. Create unified EU guidance for omics HTA using real-world data and adaptive models.
8. Add Annex VI with clear standards for omics technologies, including innovative omics, multi-omics, AI-based tools.

We call on the Commission, Member State Coordination Group, and stakeholders to adopt an inclusive, adaptive path, with pilots and real-world testing, to build an HTA system that delivers for innovation and patients alike.

JANE-2 stands ready to co-develop annexes, templates, and pilots. The final implementing act must be flexible, science-driven, and patient-focused.

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