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Original Research

Challenges in developing a digital pathology consultation network: insights from the MELCAYA experience

Dario Di Gangi [a,1], Roberta Gugliotta [b,1], Filippo Ugolini [c], Anna Szumera-Ciećkiewicz [d,e], Llucia Alos [f], Natalia Castrejón [f], Stephan Forchhammer [g], Barbara Valeri [h], Nicolas Macagno [i], Sule Ozturk Sari [j], Ozge Hurdogan [j], Sokol Sina [k], Sylvie Fraitag [l], Valerio Gaetano Vellone [m], Chiara Trambaiolo [m], Rita Alaggio [n], Sabrina Rossi [n], Giovanni Arcuri [b], Daniela Massi [a,*,2], Claudio Conti [b,2]

[a] Section of Pathological Anatomy, Department of Health Sciences, University of Florence, Florence, Italy
[b] UOC Direzione Tecnica, ICT ed Innovazione Tecnologie Sanitarie, Fondazione Policlinico Agostino Gemelli IRCCS, Roma, Italy
[c] Histopathology and Molecular Diagnostics, Careggi University Hospital, Florence, Italy
[d] Biobank, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[e] Department of Pathology, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[f] Department of Pathology, Hospital Clínic of Barcelona, University of Barcelona, Barcelona, Spain
[g] Department of Dermatology, University Medical Center, Eberhard Karls University Tübingen, Tübingen, Germany
[h] Pathology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[i] Aix-Marseille University, Marmara Institute, INSERM, U1251, MMG, DOD-CET, Marseille, France
[j] Department of Pathology, Istanbul University Istanbul Medical Faculty, Istanbul, Türkiye
[k] Section of Pathology, Department of Diagnostics and Public Health, University of Verona, Verona, Italy
[l] Pathology Department, Necker-Enfants Malades Hospital, AP-HP, Paris, France
[m] Pathology Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy
[n] Pathology Unit, Department of Laboratories, Bambino Gesu Children's Hospital, IRCCS, Rome, Italy

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ABSTRACT

Objectives: The increasing adoption of Whole Slide Image (WSI) technology has created new opportunities for collaboration in diagnostic pathology. This study aims to describe the development, implementation, and challenges of establishing a second-opinion platform for pathology revision, focusing on improving the diagnostic assessment of melanoma in children, adolescents, and young adults (CAYA).
Methods: Two-hundred-eight melanomas and atypical melanocytic lesions from CAYA patients were retrospectively collected, resulting in 311 associated WSIs. Recognizing the rarity of these cases, patient enrollment was distributed across 11 centers spanning 6 European countries. All slides were digitalized at each participating institution and uploaded into a centralized digital platform to be reviewed.
Results: A total of 144 WSIs (46.3 %) exhibited technical defects, classified as critical, major, or minor based on their impact on WSI quality and visualization. Of these, 101 (70.1 %) showed analytical defects, while the remaining 43 (29.9 %) presented pre-analytical issues. Significant inter-center variability in file sizes was observed, reflecting differences in scanning protocols and tissue processing. Twenty-four cases (11.5 %) exhibited major discordances on melanoma vs atypical melanocytic lesions classification, underscoring the importance of centralized pathological review.
Discussion: This study highlights the challenges of obtaining standardized, high-quality WSIs in real-world settings, particularly due to the rarity of the disease and the limited availability of tissue. Thesefindings reinforce

Abbreviations: WSI, Whole Slide Imaging; DP, Digital Pathology; CAYA, Children, adolescents, and young adults; H&E, Hematoxylin and Eosin; CPMS, Clinical Patient Management System; ERN, European Reference Networks; SSM, Superficial Spreading Melanoma; RUO, Research Use Only; IVDR, In Vitro Diagnostic Medical Device Regulation; GDPR, General Data Protection Regulation; CEAVC, Comitato Etico Regione Toscana-Area Vasta Centro.

* Correspondence to: Section of Pathology, Department of Health Sciences, University of Florence, Viale Pieraccini 6. Florence 50139, Italy.
E-mail address: daniela.massi@unifi.it (D. Massi).

[1] These authors equally contributed.
[2] These authors equally contributed.

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the importance of establishing standardized protocols across institutions to provide pathologists with a high-quality repository and improve patient outcome through effective second-opinion reviews.

1. Introduction

In an era of ongoing technological innovation, Digital Pathology (DP) is transforming diagnostics routine [1]. The onset of Whole Slide Imaging (WSI), based on digitalizing histopathological slides, underscores the importance of second-opinion platforms that connect experts globally for collaborative case review and discussions.[1,2]. High-resolution scanning enables the creation of detailed WSIs, revolutionizing traditional diagnostic procedures by integrating them into digitalized workflows [3].

Melanoma represents a critical health concern in childhood and adolescence [4–6]. Melanoma in childhood, adolescence and young adult (CAYA) patients poses diagnostic challenges due to distinct clinical presentations and diagnostic complexities [5,7,8]. Epidemiological data reveal that the incidence of melanoma in children under 15 years of age is 1.3–1.6 per million, increasing to 15 per million in individuals aged 15–19 [8–10]. Since 1997, the incidence among adolescents has risen by 4.1 % annually [7,9].

In this context, an example of this innovation is the European MELCAYA project (https://www.melcaya.eu), which aims to enhance the investigation of melanoma in CAYA patients. The MELCAYA study aims to improve the preventive, diagnostic, and therapeutic strategies for CAYA melanoma. The MELCAYA project addresses these challenges by promoting international collaboration and standards, and developing a new melanoma taxonomy for CAYA patients aligned with recent WHO classification updates [11]. A key element of the project is a second-opinion platform for pathologist collaboration. By connecting pathology experts through a unified platform, this project aims to ensure comprehensive access to expert consultations and establish a diagnostic standard for melanoma in CAYA.

The MELCAYA project uses a second opinion platform for histopathological review, though promising, these technologies face challenges such as managing large WSI volumes, ensuring image quality, and addressing issues in slide scanning and preparation [12]. Clinical guidelines from the College of American Pathologists and ESDIP highlight the need for standardized sample preparation and robust validation protocols [1,12–14]. Additional challenges include the need for a unified patient registry, secure data handling per GDPR standards, and workflow optimization [13,15].

This study aimed to identify key obstacles and challenges in WSIs collection, proposes quality-controlled feedback mechanisms, and emphasizes regulatory considerations to generalize its findings for developing a second opinion pathology consultation network that ensures safety, reliability, and effectiveness.

2. Material and methods

2.1. Study cohort

208 melanomas and atypical melanocytic lesions in CAYA patients were retrospectively collected, with 311 representative Hematoxylin and Eosin (H&E) associated WSIs. Due to the rarity of the pathology, the enrollment of patients and the collection of WSIs is still ongoing, involving 11 different centers from 6 countries.

To date, WSIs and patient data have been collected as follows: 22 patients (27 WSIs) from France (Aix Marseille University, Assistance Publique des Hôpitaux de Marseille, Hôpital Necker-Enfants Malades); 21 patients (21 WSIs) from Germany (Eberhard Karls University of Tübingen); 69 patients (157 WSIs) from Italy (University of Florence, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Bambino Gesù Children's Hospital IRCCS, University of Verona, IRCCS Istituto Giannina Gaslini); 10 patients (11 WSIs) from Poland (Maria Sklodowska-Curie National Research Institute of Oncology); 66 patients (66 WSIs) from Spain (Hospital Clinic de Barcelona); and 20 patients (29 WSIs) from Turkey (University of Istanbul). WSI collection lasted 19 months (Suppl. Fig. 1SA). All slides were digitized by participating centers and uploaded to the University of Florence (UNIFI) institutional drive. Each WSIs was then imported into the HALO Link® (Indica Labs, Albuquerque, NM, USA) image-management system.

2.2. Second opinion platform

Due to WSI sizes (0.5–4 GB), a solution was needed to efficiently manage large volumes of data while maintaining rapid access and retrieval capabilities. The platform needed to support various WSI formats to ensure compatibility. This required a system supporting multiple users, providing robust annotation tools, and enabling standardized reporting methods.

The first platform evaluated was the Clinical Patient Management System (CPMS). CPMS is a web-based application that supports European Reference Networks (ERN). However, the platform has some weaknesses, particularly regarding its histopathological slide viewer. The plugin reduces image quality by converting WSI into hierarchical TIFF files, making navigation inside slides less fluid. To address this limitation, a parallel digital platform is necessary to manage original WSI files. Designed with dedicated storage and management systems for WSI, would provide several benefits for the project:

- Seamless WSI navigation;
- Upload of multiple slides per case
- Annotation and measurement tools
- Advanced image analysis, such as evaluating cellular density and spatial distribution.

Based on these considerations, the MELCAYA consortium adopted a browser-based third-party software (HALO Link® Indica Labs, Albuquerque, NM, USA). The platform's quantitative analysis capabilities, particularly its integration of deep learning neural networks for image analysis, provided the tools for detailed WSI analysis. It was verified that the platform can support images in "non-proprietary" formats like JPEG, TIF, and proprietary formats like SVS, AFI, DCM, ND2, VSI, CZI, BIF, KFB, ISYNTAX, I2SYNTAX. Through HALO Link, digital slides could be shared allowing MELCAYA Pathology Board to access the images during real-time discussions. This approach ensures consistent visualization quality and supports coordinated classification assessment.

2.3. WSIs collection

UNIFI coordinated the collection of WSIs from all participating centers. Each center was requested to submit one representative H&E WSI per patient into an institutional drive. Each center was granted access to a dedicated sub-folder for uploading their WSIs and access was restricted preventing inter-center access. This solution enabled asynchronous upload and provided a secure online repository. Following quality control, performed by UNIFI personnel, the WSIs were uploaded to the second opinion platform (Fig. 1). Each center received unique codes, and WSIs were renamed accordingly, to create a progressive "MELCAYA ID". To enable comparison of scanning methods across centers, a survey was administrated to the participating countries. The survey gathered data on scanner models, magnification, and file formats.

2.4. Cases revision

For each case, the referral diagnosis provided by the submitting pathologist was recorded. All cases were reviewed by the MELCAYA Pathology Board and classified as either melanoma or atypical melanocytic lesion. Diagnostic concordance was defined as the number of cases in which the diagnosis made by the referring pathologist matched the classification assigned by the MELCAYA Pathology Board. Discordances between the referring institution and the MELCAYA Pathology Board were categorized as either major or minor. Major discordance was defined as a reclassification between melanoma and atypical melanocytic lesions. Minor discordance referred to changes in histological subtype within the same diagnostic category that did not affect the overall classification. Cases with overlapping or clinically equivalent diagnoses were considered concordant.

2.5. Statistical analysis

The statistical analysis and visualization were performed using MATLAB R2023b. The descriptive statistics for each center were calculated and Kruskal-Wallis test and post hoc comparisons with the Tukey test were performed both regarding file size in GB (raw data) and considering normalization in GB/mm^2.

The Kruskal-Wallis test was selected as the primary statistical method due to its non-parametric properties, rendering it appropriate for group comparisons without normality assumptions. Subsequent post-hoc analysis employed Tukey's test with $\alpha = 0.01$, implementing controls for multiple comparisons to identify specific inter-group variations.

3. Results

3.1. WSIs collection

To date, 208 patients have been enrolled in the MELCAYA project, each with at least one H&E WSI (Fig. 2A). Most centers submitted additional WSIs for a total of 311 WSIs (Fig. 2B). A total of 144 WSIs (46.3 %) exhibited technical defects. 101 WSIs (70.1 %) showed analytical defects related to the digitalization process, including out-of-focus images (51/101 cases, 50.5 %), scanning artifacts (23/101 cases, 22.8 %), and white balance errors (27/101 cases, 26.7 %), as shown in Suppl. Fig. 1SB. The remaining 43 WSIs (29.9 %) presented pre-analytical defects such as air bubbles (6/43 cases, 14.0 %), tissue tearing (31/43 cases, 72.0 %), and uneven slide preparation (6/43 cases, 14.0 %), as shown in Suppl. Fig. 1SC. Additionally, 77 cases were lacking proper anonymization, leading to their removal and a request for re-digitalization.

Defects were classified as critical (out of focus), major (scanning artifacts/white balance errors), and minor (pre-analytical defects), based on their impact on WSI quality upon visualization (Fig. 2C). Critical defects required rescanning due to severely impairing tissue assessment. Major defects, while not mandating rescanning, significantly impaired slide interpretation and reduced workflow efficiency. Minor defects caused localized visual noise, slowing evaluation. When possible new sections were cut, re-stained, and/or re-scanned to enhance image quality. The analysis of WSI file sizes across European centers reveals considerable variability, with raw values ranging from 0.01 GB to 6.53 GB. This variability in digital slide sizes represents a critical factor, as it directly impacts the technical requirements and storage capacity a second opinion platform must support. Based on raw data (Suppl. Fig. 2S), centers showed significant differences in file sizes (Suppl. Table 1S). The Kruskal-Wallis test confirmed these differences ($p < 0.001$), while post hoc analysis identified significant pairwise comparisons ($p < 0.01$) between centers (Suppl. Table 2S). However, when data are normalized by the analyzed tissue area (GB/mm^2) (Table 1), the distribution pattern changes substantially and the Kruskal Wallis test continues to reveal statistically significant differences among centers ($p < 0.001$) (Table 2). Notably Tukey's post-hoc analysis of normalized data identified only two comparisons that remain significantly different ($p < 0.01$), as shown in Table 2: Spain vs. Italy ($p < 0.001$) and Spain vs. Turkey ($p < 0.001$). This substantial reduction in significant comparisons demonstrates that many differences in raw file sizes were primarily attributable to variations in physical sample dimensions.

These results are confirmed by boxplot as shown in Fig. 3. Importantly, the number of samples varies considerably between centers, with Italy contributing the largest number of slides (n = 157), followed by Spain (n = 66), Turkey (n = 29), France (n = 27), Germany (n = 21) and Poland (n = 10). However, despite the limitation on sample size, the statistical significance indicates that the differences found are substantial and non-causal, probably due to variations in digitalization practices and tissue section properties. The survey reveals that the scanner models utilized are technically similar (Table 3). Despite magnification having been largely standardized across centers (40x magnification), variations were noted in the dimensions of the scanned area and in the image

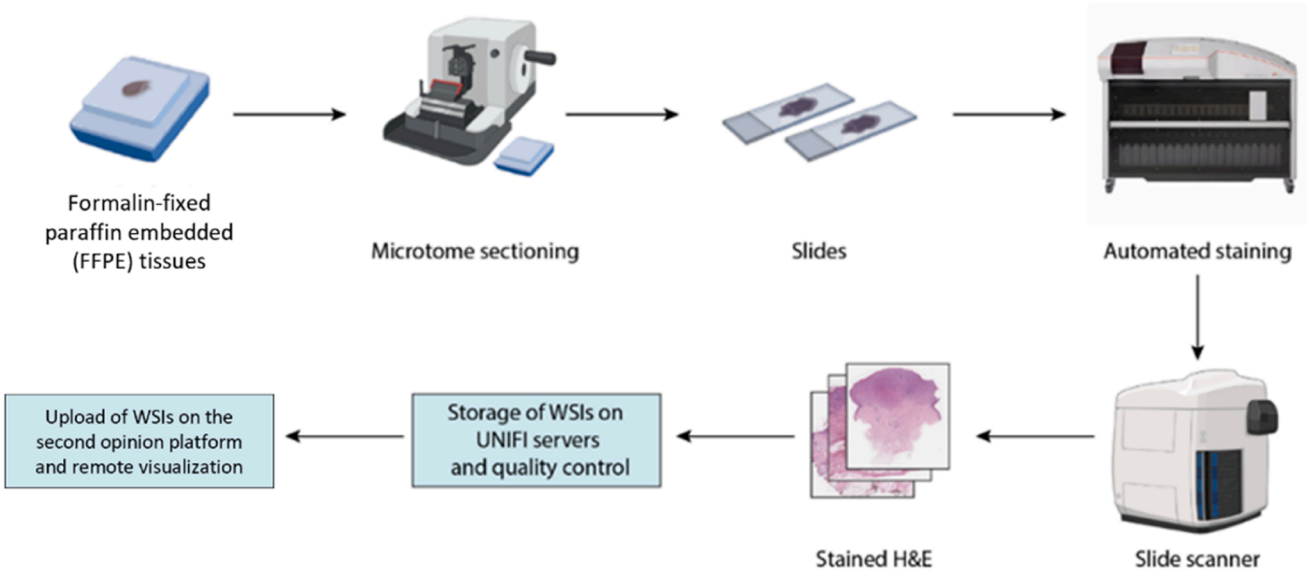

Fig. 1. Digital pathology WSIs uploading workflow.

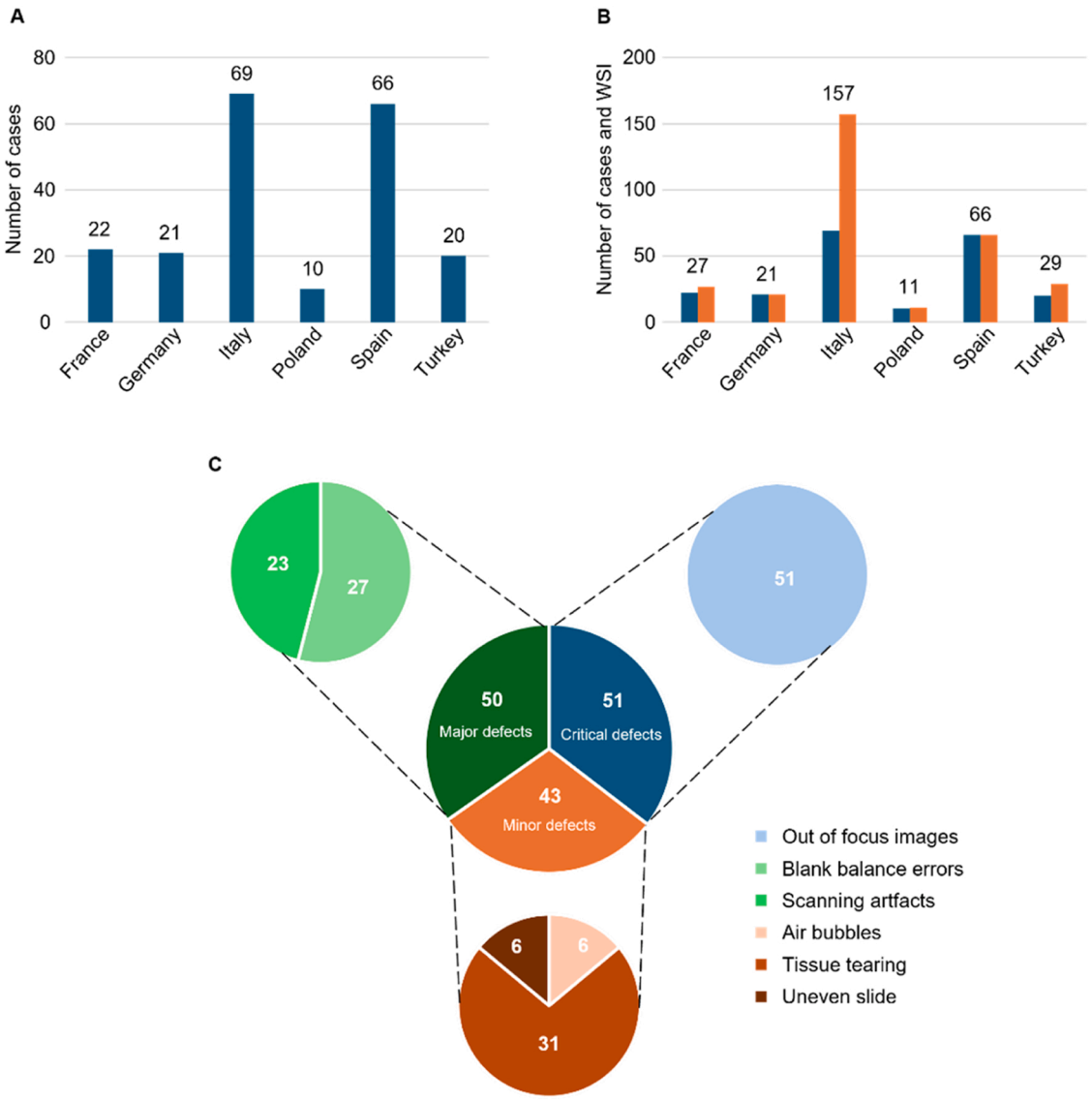

Fig. 2. A) Column chart showing the number of cases collected by each contributing country. B) Column chart displaying the number of cases (blue) and the number of WSIs (orange) collected by each center. C) Pie charts representing the types of issues observed and their distribution among three categories: critical, major and minor technical defects.

Table 1
Descriptive statistics of WSIs file size by center, normalized by tissue area.

Center	Mean normalized (GB/mm^2)	Median normalized (GB/mm^2)	Standard Deviation normalized (GB/mm^2)
FRANCE	0.0116	0.0110	0.0084
GERMANY	0.0291	0.0127	0.0443
ITALY	0.0126	0.0102	0.0134
POLAND	0.0133	0.0124	0.0048
SPAIN	0.0159	0.0140	0.0070
TURKEY	0.0087	0.0073	0.0075

Table 2
Detail of significant comparisons between centers obtained using Kruskall Wallis test ($p < 0.01$) followed by post-hoc comparisons of Tukey Test (Normalized data).

Comparison	Real Mean Difference (GB)	*p*-value
SPAIN VS. ITALY	0.003312	0.0000000300
SPAIN VS. TURKEY	0.007265	0.0000005626

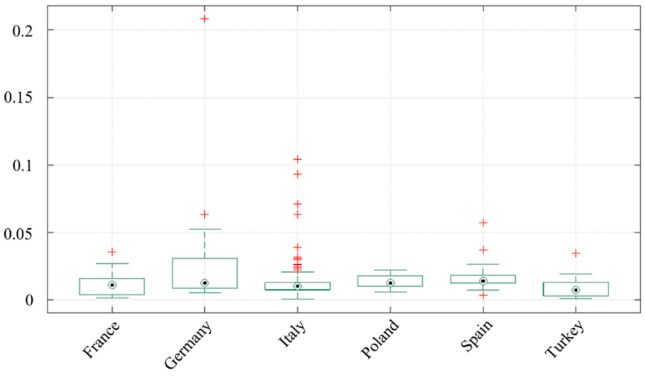

Fig. 3. Normalized data (GB/mm^2): Box-plot representation of WSIs file size for each country where the medians are represented by circles with black dots in the center, interquartile ranges are displayed as green boxes and outliers are indicated with red crosses.

Table 3
Technical specifications of scanner used: mean file sizes (GB), scanned tissue area (mm^2), scanner model magnification, and file format. Data show technological variability among digital pathology implementations with consequent differences in storage requirements and interoperability.

Center	Mean Size (GB)	Mean Total Tissue area (mm^2)	Scanner Model	Slide Magnification	File Format
FRANCE	1.19	125.12	Hamamatsu NanoZoomer 2.0 -HT (*Hamamatsu Photonics*)	60X, 40X	NDPI
GERMANY	1.21	101.88	Hamamatsu NanoZoomer 2.0 -HT (*Hamamatsu Photonics*)	40X	NDPI
ITALY	0.89	97.22	Aperio AT2 *(Leica Biosystems)* Aperio GT450DX *(Leica Biosystems)* Philips Ultra Fast Scanner (*Philips Digital Pathology Solutions*)	40X	SVS, DICOM, TIFF
POLAND	2.09	115.155	Hamamatsu NanoZoomer S360 *(Hamamatsu Photonics)*	40X	BIF, TIFF, DICOM
SPAIN	1.9	129.04	Ventana DP 600 (*Roche/ Ventana Medical Systems*)	40X	BIF, TIFF, DICOM
TURKEY	0.83	129.09	KF-PRO−020 *(KFBIO-Hangzhou Kenfubo Biotechnology)*	40X	KFB, SVS, DCM, TIFF

characteristics among different centers. These differences, combined with the scanning protocols adopted, could significantly affect the final file size. It was observed that scanning generated larger files in the following cases: multiple consecutive sections on a single slide, contiguous tissue areas that couldn't be acquired separately and presence of both primary and distant secondary fragments requiring larger scanning areas.

- Multiple consecutive sections on a single slide.
- Contiguous tissue areas that couldn't be acquired separately.
- Presence of both primary and distant secondary fragments requiring larger scanning areas.

Combined, these factors significantly affected file size.

3.2. WSIs revision

Overall, diagnostic concordance was observed in 184 of 208 cases (88.5 %). We identified 24 major discordances (11.5 %), including 11 cases (5.3 %) reclassified from melanoma to atypical melanocytic lesion and 13 cases (6.2 %) from atypical melanocytic lesion to melanoma. Minor discordances were observed in 49 of 208 cases, including 43 cases (87.8 %) involving subtype changes within melanoma and 6 cases (12.2 %) within atypical melanocytic lesion. Immunohistochemistry was performed in 110 cases (52.9 %), and molecular analyses in 98 (47.1 %). Among the 208 cases, 170 (81.7 %) were confirmed as melanoma and subclassified by the MELCAYA Pathology Board according to the most recent WHO classification as follows: Superficial Spreading Melanoma (SSM)/Low-CSD Melanoma: 80/170 (47.0 %), Spitz Melanoma: 29/170 (17.1 %), Nodular Melanoma: 24/170 (14.1 %), Melanoma on Congenital Nevus: 14/170 (8.2 %), Nevoid Melanoma: 8/170 (4.7 %), Metastatic Melanoma: 7/170 (4.1 %), Spitzoid Melanoma: 2/170 (1.2 %), Blue Nevus-like Melanoma: 2/170 (1.2 %), Melanoma in situ: 2/170 (1.2 %), Acral Melanoma: 1/170 (0.6 %), Melanoma, NOS: 1/170 (0.6 %). The remaining 38 cases (18.3 %) were classified as atypical melanocytic lesion. These cases are currently undergoing further molecular characterization and will be subclassified accordingly based on the results.

4. Discussion

By leveraging WSI technology, a dedicated second-opinion platform, and a centralized WSI repository, this initiative has fostered a collaborative network that enhances histopathological assessments' accuracy, reproducibility, and efficiency across multiple institutions. A key achievement of the project was the establishment of a European WSI repository, enabling seamless inter-institutional consultation and standardization of atypical melanocytic lesion diagnoses in CAYA patients. To achieve this aim, a pathology consultation network was created between UNIFI and 10 collaborating institutions. The collection process was slow, requiring 19 months. Several factors contributed to this extended timeline [16]. First, due to the rarity of the disease and the limited availability of material, each institution had to carefully select suitable cases, which were then reviewed by the MELCAYA pathology board. Following this review, some institutions were required to rescan cases to meet the established quality criteria.

Quality control revealed frequent artifacts and scanning issues, common in WSI workflows [16–18]. Among the 311 WSIs collected, 144 WSIs (46.3 %) exhibited at least one defect. Defects were categorized into three groups: critical, major and minor based on the extent to which they impacted the evaluation of the WSIs, emphasizing the need for a standardized protocol across the institutions.

The management of WSIs posed significant technical and organizational challenges [16,19]. Despite the wide variability in file sizes and the statistically significant differences observed across centers, the platform successfully supported the upload of all digital slides included in the study. However, for slides exceeding 4 GB, the standard web-based upload process had to be bypassed in favor of local uploads. These findings are particularly relevant for planning the storage infrastructure required to support DP platforms. Storage systems should be dimensioned to accommodate files of diverse sizes, ensuring that the maximum observed size (6.53 GB) is considered as a benchmark to guarantee full compatibility. Statistical analysis performed on the collected WSIs size, showed how the differences in the mean size of WSIs among different centers was non-casual thus suggesting the presence of different and non-standardized protocols for the preparation of slides and WSIs acquisition. Despite the technical similarity in scanner models and magnification used across centers, some outliers remained after normalization. These cases were associated with specific slide characteristics, such as multiple tissue sections, non-adjacent fragments, or contiguous tissue portions, that required scanning of larger areas. These features, along with differences in the scanning protocols, likely account for the increased file sizes observed.

The proposed second-opinion platform offered several advantages, in line with the system proposed by Hanna et al. using the Omnyx platform [20]. One of the key benefits was its 24/7 availability, allowing independent and concurrent WSI uploads. This also enabled simultaneous WSI consultations and overnight uploads of large file volumes without disrupting routine daily institutional activities. Another major advantage was multi-format compatibility, a crucial feature since different

scanner models that generate different WSI formats. Additionally, the ability to annotate, comment on, and visualize WSIs remotely improved collaboration among pathologists.

Despite these benefits, the platform also had limitations. A major drawback was that HALO Link is a Research Use Only (RUO) platform, imposing constraints on system implementation. Regulatory considerations arise under the new European In Vitro Diagnostic Medical Device Regulation (IVDR - EU 2017/746) [21,22]. Additionally, compliance with privacy and data security regulations particularly the General Data Protection Regulation (GDPR-EU 2016/679) [23] posed a significant challenge. The classification of WSIs remains a subject of debate in the research community. While some consider WSIs low-risk data suitable for open repositories, the MELCAYA study classified them as sensitive clinical data, requiring strict confidentiality protocols [24]. According to this perspective, WSIs should be treated with the same privacy standards as other medical records and disseminated only as pseudonymized datasets [25,26]. As a result, many slides were discarded due to improper anonymization and lack of compliance with patient privacy regulations. Under Article 9.2(h) and Article 9.2(i) of the GDPR, the processing of special categories of personal data, including health data, is permitted for healthcare and public health purposes, provided that specific safeguards are in place [23].

These requirements intersect with both GDPR and IVDR regulations, creating a complex regulatory landscape. In the context of the MELCAYA project, this significantly impacts the development and implementation of DP solutions. Healthcare institutions must carefully balance the innovative potential of DP platforms with regulatory compliance, ensuring both scientific validity and legal adherence [27–30].

This study highlights the challenges of obtaining standardized, high-quality WSIs in real-world settings, particularly due to the rarity of the disease and limited tissue availability. These findings underscore the need for standardized protocols across institutions to ensure a high-quality digital repository and support accurate second-opinion reviews.

CRediT authorship contribution statement

Rita Alaggio: Data curation. **Llucia Alos:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Trambaiolo Antonelli Chiara:** Data curation. **Anna Szumera-Ciećkiewicz:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Valerio Gaetano Vellone:** Data curation. **Sylvie Fraitag:** Data curation. **Roberta Gugliotta:** Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation. **Sokol Sina:** Data curation. **Dario Di Gangi:** Writing – original draft, Methodology, Investigation, Data curation. **Ozge Hurdogan:** Data curation. **Sule Ozturk Sari:** Data curation. **Claudio Conti:** Writing – review & editing, Supervision, Software, Resources, Funding acquisition, Conceptualization. **Nicolas Macagno:** Data curation. **Daniela Massi:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Barbara Valeri:** Data curation. **Giovanni Arcuri:** Software. **Stephan Forchhammer:** Data curation. **Sabrina Rossi:** Data curation. **Castrejòn Natalia:** Writing – original draft, Investigation. **Filippo Ugolini:** Writing – original draft, Writing – review & editing, Investigation.

Ethics approval

The use of WSIs produced by the scanning process of patient's histopathological slides was approved by the Local Ethics Committee "Comitato Etico Regione Toscana-Area Vasta Centro (CEAVC)" (24680_bio). This study was performed in accordance with the Declaration of Helsinki.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejcskn.2025.100742.

References

[1] P.C. Rizzo, A. Caputo, E. Maddalena, N. Caldonazzi, I. Girolami, A.P. Dei Tos, et al., Digital pathology world tour, Digit Health 9 (2023), https://doi.org/10.1177/20552076231194551.
[2] B.L. Liu, M. Haghighi, W.H. Westra, Digital pathology is a fast and effective platform for providing head and neck pathology consultations, Am. J. Surg. Pathol. 48 (2024) 985–990, https://doi.org/10.1097/PAS.0000000000002239.
[3] H.U. Voelker, L. Poetzl, A. Strehl, H.K. Mueller-Hermelink, A. Stuefe, G. Stauch, Telepathological evaluation of paediatric histological specimens in support of a hospital in Tanzania, Afr. Health Sci. 20 (2020) 1313–1321, https://doi.org/10.4314/ahs.v20i3.37.
[4] C.D. Downard, L.B. Rapkin, K.W. Gow, Melanoma in children and adolescents, Surg. Oncol. 16 (2007) 215–220, https://doi.org/10.1016/j.suronc.2007.09.006.
[5] K.M. Cordoro, D. Gupta, I.J. Frieden, T. McCalmont, M. Kashani-Sabet, Pediatric melanoma: results of a large cohort study and proposal for modified ABCD detection criteria for children, J. Am. Acad. Dermatol. 68 (2013) 913–925, https://doi.org/10.1016/j.jaad.2012.12.953.
[6] M. Mandalà, A. Ferrari, I.B. Brecht, K.P. Suijkerbuijk, L. Maschke, D. Giannarelli, et al., Efficacy of anti PD-1 therapy in children and adolescent melanoma patients (MELCAYA study), Eur. J. Cancer 211 (2024) 10–15, https://doi.org/10.1016/j.ejca.2024.114305.
[7] D. Han, J.S. Zager, G. Han, S.S. Marzban, C.A. Puleo, A.A. Sarnaik, et al., The unique clinical characteristics of melanoma diagnosed in children, Ann. Surg. Oncol. 123 (2012) 40–43, https://doi.org/10.1245/s10434-012-2554-5.The.
[8] A. Indini, F. Didoné, D. Massi, S. Puig, J.R. Casadevall, D. Bennett, et al., Incidence and prognosis of cutaneous melanoma in european adolescents and young adults (AYAs): EUROCARE-6 retrospective cohort results, Eur. J. Cancer 213 (2024), https://doi.org/10.1016/j.ejca.2024.115079.
[9] M. de Vries, W.G. Vonkeman, R.J. van Ginkel, H.J. Hoekstra, Morbidity after inguinal sentinel lymph node biopsy and completion lymph node dissection in patients with cutaneous melanoma, Eur. J. Surg. Oncol. 32 (2006) 785–789, https://doi.org/10.1016/j.ejso.2006.05.003.
[10] A. Ferrari, I.B. Brecht, G. Gatta, D.T. Schneider, D. Orbach, G. Cecchetto, et al., Defining and listing very rare cancers of paediatric age: consensus of the joint action on rare cancers in cooperation with the european cooperative study group for pediatric rare tumors, Eur. J. Cancer 110 (2019) 120–126, https://doi.org/10.1016/j.ejca.2018.12.031.
[11] D.E. Elder, B.C. Bastian, I.A. Cree, D. Massi, R.A. Scolyer, The 2018 world health organization classification of cutaneous, mucosal, and uveal melanoma detailed analysis of 9 distinct subtypes defined by their evolutionary pathway, Arch. Pathol. Lab Med 144 (2020) 500–522, https://doi.org/10.5858/arpa.2019-0561-RA.
[12] L. Pantanowitz, K. Dickinson, A.J. Evans, L.A. Hassell, W.H. Henricks, J.K. Lennerz, et al., American telemedicine association clinical guidelines for telepathology, J. Pathol. Inf. 5 (2014) 39, https://doi.org/10.4103/2153-3539.143329.
[13] M.D. Herrmann, J.K. Lennerz, Technical, operational, and regulatory considerations for the adoption of digital and computational pathology, Pathologe 41 (2) (2020) 103–110, https://doi.org/10.1007/s00292-020-00871-z.
[14] F. Fraggetta, V. L'imperio, D. Ameisen, R. Carvalho, S. Leh, T.R. Kiehl, et al., Best practice recommendations for the implementation of a digital pathology workflow in the anatomic pathology laboratory by the european society of digital and integrative pathology (ESDIP), Diagnostics 11 (2021), https://doi.org/10.3390/diagnostics11112167.
[15] J. Temprana-Salvador, P. López-García, J.C. Vives, L. de Haro, E. Ballesta, M. R. Abusleme, et al., DigiPatICS: digital pathology transformation of the Catalan health institute network of 8 Hospitals—Planification, implementation, and preliminary results, MDPI Diagn. 12 (2022), https://doi.org/10.3390/diagnostics12040852.
[16] A. Baidoshvili, N. Stathonikos, G. Freling, J. Bart, N. 't Hart, J. van der Laak, et al., Validation of a whole-slide image-based teleconsultation network, Histopathology 73 (2018) 777–783, https://doi.org/10.1111/his.13673.
[17] V. Kanwar, A. Woicik, B. Dulken, C. Probert, Z.R. Mccaw, Multi-Artifact detection and filtering in digital pathology using intrinsic image properties, Proc. Int. Symp Biomed. Imaging (2024) 1–5, https://doi.org/10.1109/ISBI56570.2024.10635902.

[18] C. Senaras, M. Khalid Khan Niazi, G. Lozanski, M.N. Gurcan, DeepFocus: detection of out-of-focus regions in whole slide digital images using deep learning, PLoS One 13 (2018) 1–13, https://doi.org/10.1371/journal.pone.0205387.
[19] T. Chong, F. Palma-Diaz M, C. Fisher, D. Gui, N. L. Ostrzega, G. Sempa, et al., The california telepathology service: UCLA's experience in deploying a regional digital pathology subspecialty consultation network, J. Pathol. Inf. 9 (2019) 1–6, https://doi.org/10.4103/jpi.jpi.
[20] M.G. Hanna, L. Pantanowitz, Feasibility of using the omnyx digital pathology system for cytology practice, J. Am. Soc. Cytopathol. 8 (2019) 182–189, https://doi.org/10.1016/j.jasc.2019.01.003.
[21] The European Parliament and the Council of the European Union, Regulation (EU) 2017/746 of the european parliament and of the council on in vitro diagnostic medical devices and repealing directive 98/79/EC and commission decision 2010/227/EU, Off. J. Eur. Union 5 (2017) 117–176.
[22] A. Kahles, H. Goldschmid, A.L. Volckmar, C. Ploeger, D. Kazdal, R. Penzel, et al., Structure and content of the EU-IVDR: current status and implications for pathology, Pathologie 44 (2023) 73–85, https://doi.org/10.1007/s00292-022-01176-z.
[23] European Union, 2016 regulation (EU) no. 2016/679 of the european parliament and of the council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data (General Data Protection Regulation), in: Official Journal of the European Union, 119, 2016, pp. 1–88.
[24] P. Holub, H. Müller, T. Bíl, L. Pireddu, M. Plass, F. Prasser, et al., Privacy risks of whole-slide image sharing in digital pathology, Nat. Commun. 14 (2023), https://doi.org/10.1038/s41467-023-37991-y.
[25] F. McKay, B.J. Williams, G. Prestwich, D. Bansal, N. Hallowell, D. Treanor, The ethical challenges of artificial intelligence-driven digital pathology, J. Pathol. Clin. Res. 8 (2022) 209–216, https://doi.org/10.1002/cjp2.263.
[26] Confidentiality, Good practice in handling patient information, Gen. Med. Counc. (2017).
[27] D.S. Char, N.H. Shah, D. Magnus, Implementing machine learning in health care — addressing ethical challenges, N. Engl. J. Med. 378 (2018) 981–983, https://doi.org/10.1056/nejmp1714229.
[28] I.I.W. Nicholson Price, I. Glenn Cohen, Privacy in the age of medical big data, Physiol. Behav. 176 (2017) 100–106, https://doi.org/10.1177/0022146515594631.Marriage.
[29] A. Kahles, H. Goldschmid, A.-L. Volckmar, C. Ploeger, D. Kazdal, R. Penzel, et al., Regulation (EU) 2017/746 (IVDR): practical implementation of annex I in pathology, Die Pathol. 44 (2023) 86–95, https://doi.org/10.1007/s00292-023-01274-6.
[30] P. Refolo, C. Raimondi, L. Battaglia, J.M. Borràs, P. Closa, A. Lo Scalzo, et al., Policy challenges in Ultra-Rare cancers: ethical, social, and legal implications of melanoma prevention and diagnosis in children, adolescents, and young adults, Healthcare 13 (2025) 1–17, https://doi.org/10.3390/healthcare13030321.