Cancer Research Collaboration Grant Year 1 progress report (April 2024)

The Legacy to Life program is going very well with Cancer Research Collaboration support. Below are the stated objectives of the project and progress to date.

Overarching goal: Collect and preserve autopsy samples from metastatic cancer patients for multi-level analysis. Identification of cases has been a productive collaborative effort between medical oncologists, the patient and next of kin, other clinical caretakers, a social worker, and our team (anatomical pathologists and scientists).

A. Autopsy arrangement and preparation. We hired a talented social worker, Lisa Gauchay (0.5 FTE), with experience in end-of-life planning for metastatic cancer patients. She has set up the following processes: Once a patient has expressed interest in participating in Legacy to Life, Lisa works closely with the patient and next-of-kin to make arrangements. This includes the informed consent process including legal paperwork to express the patient's wishes to participate in the program, the autopsy consent, funeral home coordination and payment, arrangement for on-call staff in Pathology, and family instructions for the time of death. Our autopsy procedure, by necessity, is rapid and does not interfere with subsequent funeral procedures including viewing, and we work with the next of kin to ensure their wishes are honored.
B. Specimen collection. The autopsy is standard, except that it occurs shortly after death, and is conducted by licensed personnel in Pathology/ARUP at the University of Utah School of Medicine. Thanks to CRC funds, we can now pay for on-call time for pathology 24/7 to conduct rapid autopsies. My research staff also attend the autopsy to facilitate collection of the appropriate tissue samples according to a pre-determined autopsy plan based on the clinical chart and imaging data in each case. Specimen collection is comprehensive and forward-thinking to advance both this proposal and future analyses. We collect fresh, frozen, and fixed specimens from all affected sites (known metastases and uninvolved tissue that we hypothesize contains dormant cancer cells). Even if apparently unaffected, we collect samples of bone marrow, lung, brain, and liver – these are reported sites for dormant cancer cells at nearly 100% frequency in people who have died of metastatic cancer. In addition to sample collection for genomics, samples will be prepped for single cell RNA sequencing and proteomics and spatial RNA sequencing. Fresh samples are developed into living models whenever possible, allowing future studies with viable derivatives from these precious cases.

Progress to date is illustrated in this chart:

Progress	As of 20 April 2024
# of Legacy to Life patients (consented)	16
# of Legacy to Life patients who died	11
# of Legacy to Life patients autopsied	8
# of Legacy to Life patients still living	5
total # of Legacy to Life tissue samples collected	929*
median # of tissue samples per case	90*
range of # of tissue samples per case	62-304*

*cases 1-7; case 8 data is still pending analysis

This year we also became founding members of a new international consortium to develop best practices for research autopsies. We published a paper in March 2024 (appended to this report) and were proud to include acknowledgement of the CRC support in that publication.

Our goals for next year are to continue to hone best practices, to continue to conduct rapid autopsy tissues for our studies, and to start to utilize some of the materials to answer research questions that are funded by other granting mechanisms.

Thank you for your support!
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ORIGINAL ARTICLE

Research autopsy programmes in oncology: shared experience from 14 centres across the world

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Abstract

While there is a great clinical need to understand the biology of metastatic cancer in order to treat it more effectively, research is hampered by limited sample availability. Research autopsy programmes can crucially advance the field through synchronous, extensive, and high-volume sample collection. However, it remains an underused strategy in translational research. Via an extensive questionnaire, we collected information on the study design, enrolment strategy, study conduct, sample and data management, and challenges and opportunities of research autopsy programmes in oncology worldwide. Fourteen programmes participated in this study. Eight programmes operated 24 h/7 days, resulting in a lower median postmortem interval (time between death and start of the autopsy, 4 h) compared with those operating during working hours (9 h). Most programmes ($n = 10$) succeeded in collecting all samples within a median of 12 h after death. A large number of tumour sites were sampled during each autopsy (median 15.5 per patient). The median number of samples collected per patient was 58, including different processing methods for tumour samples but also non-tumour tissues and liquid biopsies. Unique biological insights derived from these samples included metastatic progression, treatment resistance, disease heterogeneity, tumour dormancy, interactions with the tumour micro-environment, and tumour representation in liquid biopsies. Tumour patient-derived xenograft (PDX) or organoid (PDO) models were additionally established, allowing for drug discovery and treatment sensitivity assays. Apart from the opportunities and achievements, we also present the challenges related with postmortem sample collections and strategies to overcome them, based on the shared experience of these 14

programmes. Through this work, we hope to increase the transparency of postmortem tissue donation, to encourage and aid the creation of new programmes, and to foster collaborations on these unique sample collections.

Keywords: research autopsy; tissue donation; metastatic cancer; tumour model; liquid biopsy

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Introduction

Metastatic disease is the main cause of death from cancer and is currently almost always incurable [1]. The multi-step progression from early to metastatic cancer has been described for some tumour types (reviewed in [2–5]). However, many of the steps in the cascade are still poorly understood from a biological point of view [2]. Additionally, inter- and intra-patient tumour heterogeneity is increasingly being described at the (epi)genomic, transcriptomic, phenotypic, and micro-environmental levels [6–11], and complicates the clinical management of metastatic disease [12].

A better biological understanding of metastatic cancer is key to advancing the clinical management of cancer patients. The goals of research include the discovery of features shared by all metastases that are efficiently targetable, of ways to reduce intra-tumour heterogeneity, or of mutually exclusive mechanisms that can be targeted through combination strategies. This requires comprehensive studies of multiple samples per patient at multiple points in time. Unfortunately, obtaining a biopsy from a metastatic site is often not possible due to their anatomical localisation and the invasiveness of the procedure. Even when technically feasible, the biopsy may not be representative of the full tumour profile. Liquid biopsies, such as blood samples, can represent an elegant way of sampling a more complete tumour profile, but to what extent different metastases contribute has so far been studied only in small cohorts [13–15].

Research autopsies, aimed at collecting multiple patient samples within a short timeframe after death for the specific purpose of translational research, constitute an invaluable answer to this problem. Also termed rapid autopsy or postmortem tissue donation programmes, they importantly differ from clinical autopsies not only in their goals but also in their organisation [16–20]. The concept is not new and has been of great value in areas of research in which access to samples is problematic

during life, such as neurological [21–25] and chronic (infectious) diseases [26,27]. More recently, research autopsies have also been used to help to understand organ damage from COVID-19 [19,28–30]. In oncology, multiple excellent autopsy programmes have been developed and have described their structure and logistics of approach [11,16–18,31–38]. Most publications are, however, single programme reports and do not compare methodologies across locations in a structured way [16,32,38]. The research autopsy as a method of enhancing access to tissue samples is also still under-utilised. This study evaluated 14 research autopsy programmes in oncology worldwide to identify commonalities, important logistical aspects of tissue donation, and ethical considerations. Experience gained in these studies may be informative for increasing transparency, enhancing worldwide interdisciplinary collaborative research, as well as for the initiation of new programmes and expansion of existing programmes.

Materials and methods

Ethics approval statement

Each programme has its respective ethics approval and patient consent for participation.

A questionnaire with over 150 questions on five topics (study design, patient enrolment, study conduct and tissue donation procedure, sample and data management, and challenges and opportunities) was designed for this study (supplementary material, Table S1). Research autopsy programmes in oncology were identified based on literature reviews, clinical trial databases, and professional networks. Programmes temporarily on hold were eligible, while programmes for paediatric patients (which generally have distinct inclusion procedures) or pure clinical autopsy programmes were excluded. Programmes were contacted via e-mail, and follow-up meetings after questionnaire completion were conducted to clarify uncertainties and to ensure data completeness across the topics. No ethical approval was needed for this study. Information was retrieved between December 2022 and May 2023. The results are presented in a descriptive manner.

Results

Presentation of the included programmes

Twenty-eight programmes were identified, of which 23 were contacted after revision of inclusion criteria (supplementary material, Figure S1). Of these, 14 provided us with their data within the set timeframe. Though a majority ($n = 9$) were based in the USA (Figure 1A), others from the United Kingdom, Belgium, Hungary, Australia, and Japan ($n = 1$ in each country) were included. The main characteristics of the respective programmes are listed in supplementary material, Table S2. Of note, none of the 23 identified programmes were in South America or Africa.

All principal investigators ($n = 14$) had academic positions. The programme set-up was led by a research team in eight, a clinical team in two, and a combination of both in four programmes. Most programmes followed institutional ethics committee-approved research protocols as required by their legal and ethical framework for research on deceased patients. Some studies formalised their protocol after conducting sporadic research autopsies at patients' requests ($n = 6$). Others spent a median of 12 months (range 6–48 months) of logistic and administrative preparatory work before any autopsy was performed. The legal framework influenced the establishment and conduct of some of the autopsy programmes. The PEACE (Posthumous Evaluation of Advanced Cancer Environment) programme, for example, experienced autopsy delays due to strict regulations regarding the signature of death certificates. The UPTIDER (UZ/KU Leuven Program for Tissue Donation to Enhance Research), Genitourinary Cancer Biorepository, Legacy Project for Rapid Tissue Donation, and CASCADE (CAncer tiSsue Collection After DEath) programmes operated in regions where assisted dying was or became authorised, enabling preplanning of the autopsy if the patient chose euthanasia (which occurred in 25%, <10%, 8%, and 3% of patients in these programmes, respectively).

The programmes primarily focused on collecting metastatic and non-tumour tissues to allow diverse lines of research. Research objectives built on this focused on cancer heterogeneity, tumour evolution, tumour micro-environment, mechanisms of treatment response/resistance, representability of liquid biopsies, and creation of experimental tumour models. Additionally, some programmes supported research in other diseases or areas, through the sharing of samples or of experience for the creation of other programmes.

All programmes adopted a multidisciplinary approach with high involvement of the Departments of Pathology and General Medical Oncology (in $n = 14$ and $n = 13$ programmes, respectively). Of note, the number of pathologists involved varies according to the programme: most have a pool of three or four pathologists on rota, while others have dedicated pathologists in the programme or are (co)-led by pathologists. Many programmes additionally collaborated with other clinical and academic partners, both within their institution and externally.

Patient inclusion and follow-up

Six programmes enrolled patients with any primary cancer type (Figure 1B and supplementary material, Table S2). Three adopted a focused multi-cancer approach including only tumour types with established collaborations for maximal sample utilisation. The remaining five programmes allowed up to two primary tumour types: breast in Legacy to Life, Hope for OTHERS (Our Tissue Helping Enhance Research & Science), the UNC Breast

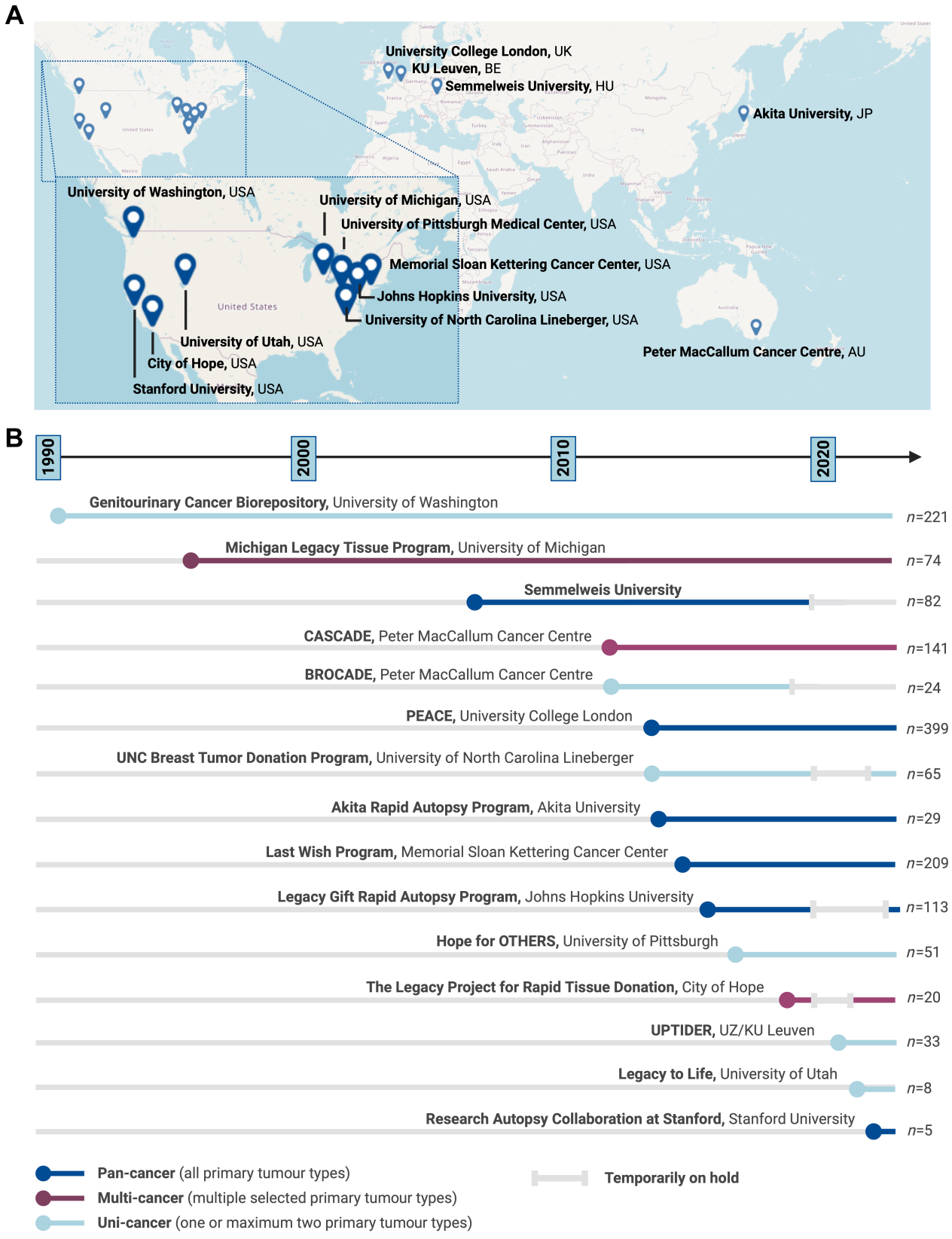

Figure 1. Overview of the programmes included in this study. (A) Map highlighting the primary locations of the programmes. (B) Timeline of the programmes. The total number of patients included until May 2023 is depicted on the right. Created with BioRender.com.

Tumour Donation program, and UPTIDER; and prostate and bladder cancer in the Genitourinary Cancer Biorepository. Of note, the multi-cancer programme CASCADE had a sister project focusing on breast cancer only (BROCADE), which will be discussed separately only if significantly differing from CASCADE.

Most programmes ($n = 12$) allowed patients dying at home to participate but put restrictions on distance from

the programme hospital. Patient referral was allowed in eight programmes, on the condition of registration in one of the enrolling centres. Patients of particular research interest due to clinical features of their cancer, i.e. genetic predisposition or specific treatments, were sometimes targeted for enrolment. However, this was never an official inclusion criterion. Most programmes ($n = 11$) did not accept patients with known communicable diseases, either chronically or acutely present at the time of death. In the other programmes, appropriate equipment and measures were used to ensure that autopsies were safely performed in these high-risk settings [19].

Informed consent was required in all programmes, signed either obligatorily by the patient ($n = 1$), by the next-of-kin/family ($n = 6$), by both ($n = 1$), or by either of the two ($n = 6$). Treating-oncologists usually first approached patients and/or their families but sometimes found it difficult to discuss end-of-life matters in their role as healthcare providers. In response to this, some programmes have allowed first conversations by psychosocially trained members of the research team. Occasionally, patients touched on the subject themselves, especially in regions where assisted dying was legal. Leaflets in hospital waiting rooms, information on the institution's website, or articles in the general press could enhance self-referral (ten programmes used this). We have listed tips for best wording to introduce and discuss the topic in Table 1.

Three inclusion strategies emerged from our survey, with corresponding timelines presented in Figure 2. Firstly, most programmes ($n = 12$) included patients in their last line(s) of treatment and/or in best supportive care setting. The median time between enrolment and death in programmes that allowed only this scenario ($n = 2$: Legacy to Life and UPTIDER) was 3 and 5 weeks, respectively. Secondly, more than half of the programmes additionally allowed inclusion in early non-curative ($n = 8$) or even curative treatment settings ($n = 3$). This answers the documented preference of patients to be active decision makers when the choice is not urgent, as with organ donation [39]. Thirdly, six programmes allowed the enrolment of patients after death, via the next-of-kin's consent. This strategy had the advantages of tailoring inclusion based on timing of death (e.g. avoiding weekend autopsies) and alignment with obtaining consent for clinical autopsies. On the other hand, there was little time for patient-specific autopsy preparation. While many countries allowed after-death next-of-kin consent, this might bring psychological discomfort to the family and researchers. The Michigan Legacy Tissue Program resolved this through after-death consent via the next-of-kin, but only after thorough discussions with the patient during life.

Apart from eligibility criteria and timing, there were other reasons not to approach patients. Seven programmes preferentially did not contact patients who were not coping well with their prognosis, were not well supported by their families, had a strained relationship with their clinicians, or had refused to participate in other research/biobanking studies in the past. Seven programmes reported an estimate on the percentage of patients who are eventually approached out of all eligible patients, with the average being 40% (range 5–80%). Of note, some patients were approached carefully but if their initial reaction to the programme was not positive, it was not mentioned thereafter.

With these inclusion strategies, enrolment of patients was highly successful. Of those who received the informed consent documents, 75% (average of the percentages in all programmes; range 40–100%) signed up. Many reasons for participation were listed by the patients including contributing to scientific advancements, helping future patients, and being offered an alternative for organ donation. The most common reason for not participating was psychosocial distress. Only one programme reported that patients were sometimes not convinced of the project's scientific value. Almost all programmes ($n = 12$) allowed opt-out from parts of the study, such as certain anatomical regions (e.g. brain) being sampled, and collaboration with non-academic partners. Patients seldom (<10% of cases in all but one programme) chose these opt-outs.

Importantly, the family played a big role in recruitment and follow-up in most programmes. Family objections because of psychosocial distress or possible impact on funeral services were reported in ten studies as a reason for not participating. In the interval between enrolment and death, programmes maintained contact with caregivers or passively followed up through medical file checks. Table 1 suggests tips for effective interaction and strategies to handle challenges during follow-up.

At death: logistics and tissue donation procedure

Eight programmes performed autopsies 24 h/7 days (Figure 3A), with associated challenges discussed in Table 1. Their median postmortem interval (PMI, between death and autopsy start) was 4 h (range of medians 2.5–14) for patients dying outside of the hospital (vast majority). In programmes restricting autopsies to (extended) working hours, the median PMI was 9 h (range of medians 4 h to 4 days). Transportation of patients who passed away outside of the hospital was performed by a company contracted specifically for the study in seven programmes. Upon arrival, the body was ideally refrigerated until the autopsy commenced. Four programmes performed imaging before the autopsy (whole body CT and/or MRI), either as part of the standard forensic procedure or as part of the research protocol.

The median number of staff present at each autopsy was 4 (range 2–13). Essential roles included a pathologist and/or a mortuary technician (officially referred to as an anatomical pathology technologist (APT) in the UK and often referred to as a morgue or autopsy technician in many other countries), a coordinator overseeing sample procurement, and research personnel handling sample processing and registration. Autopsies took

Table 1. Challenges related to rapid autopsy programmes and strategies to overcome them. Combined experience from the 14 programmes.

Challenge	Strategy/solution
Personnel challenges	
Finding skilled team members	– Multidisciplinary team – Pathologist and/or mortuary assistant are crucial and should be dedicated [if needed, third-party (private) pathology service to be added on] – Psychological skills, high flexibility, and meticulousness are of great value
Personnel turnover	– Long-term grants can help to assure job security – Having back-ups for every role makes the position more attractive/bearable – Set up a structure in which motivated people can temporarily join the team and learn
Emotional impact on team members	– Participation must be voluntary for lab personnel – Debrief shortly after an autopsy and allow for emotional difficulties to be discussed – Have a psychological care team (e.g. from hospital) available
Having at least one person on call 24 h/7 days	– Rotate this task within the team – Prerecord a message on the study phone's voicemail in case no one can answer
Motivating personnel to work outside of business hours	– Provide financial compensation – Allow job flexibility including recovery time – Involve personnel in scientific discussions and give co-authorship on publications – Show up as a supervisor/principal investigator as often as possible
Budgetary challenges	
Finding appropriate funding for personnel	– Work with research personnel already covered by other research-related grants – Work with existing (clinical) autopsy structures
Finding appropriate funding for the set-up or downstream research	– Apply for grants related to infrastructure or biospecimen acquisition – Make sure collaborators secure funding and include sample acquisition costs – Recover costs where possible (e.g. per-sample fee) – Negotiate prices where possible (transport companies, pathology services, …)
Regulatory challenges	
Discussions with the Ethics Committee (EC) including data sharing, privacy, and informed consent	– Start discussions with the EC early on when designing the programme – Involve the legal team – Consider publishing patient data in aggregated form rather than individual data – Make sure the informed consent allows creation of tumour models, genomic analyses, controlled database posting, and collaboration with non-academic partners, if applicable
Signature of the death certificate	– Make sure involved parties (general practitioner, ward physician) are aware of the urgency and of the procedure to be followed
Collaboration challenges	
Essential collaboration within the institution	– Programme to be advertised actively to colleagues (presentations, conferences)
Communication	– Rotate authorships for large teams – Organise regular and specific communication with those involved about the study conduct as well as on downstream analyses and results – Enhance collaborations between different laboratories to integrate sample data on a multi-omics level – Find an efficient way of sharing essential patient and sample information
Enrolment challenges	
Motivate physicians to include patients	– Organise meetings to discuss barriers and exchange inclusion strategies – Provide tips on the use of language and on timing – Ask permission for the study coordinator to screen and contact patients directly – Keep clinicians updated about scientific results
Patient selection and timing of enrolment	– Select patients with longitudinal samples available, included in clinical trials, or of specific research interest – Consider including early in the disease course; patients express they prefer this – Introduce the programme when the patient offers cues – Educational material in waiting rooms, allowing patients to bring up the topic
Wording used during enrolment	– Get advice from patient advocates and supportive care staff – Minimise taboo and normalise end-of-life discussions and tissue donation – Focus on the meaning their donation will have for future generations – 'Tissue donation' preferred over 'autopsy'
Involvement of the family	– Try to talk to the patient and their family in the same session – Be very transparent about the procedures, the timing, impact on the funeral, … – Consider asking for feedback from families some time after the tissue donation – Consider honouring donating patients with a section on the programme website where families can contribute
Follow-up challenges	
Knowing how and how often to follow up	– Passively follow up through patient files – Ensure patients/families are updated on procedures when life expectancy shortens – actively follow up with the supportive care team or hospice – Provide all people involved with contact cards and steps to take

(Continues)

Table 1. Continued

Challenge	Strategy/solution
Challenges related to the tissue donation procedure and sample processing	
Limiting the autopsy time and the number of staff	– Attribute specific roles – Standardise operating procedures (SOPs) and collection methods – If needed, minimise the amount of information collected per sample and reduce the number of samples per organ
Availability of the morgue and equipment in the morgue	– Back-up strategies such as university autopsy rooms – Bring any missing equipment in
Collecting all metastases	– Know upfront where bone metastases are, if sampling is desired – Decide whether to explore the brain based on previous or postmortem imaging (or CSF) – Subject the skin to careful inspection – Subject all other organs to gross dissection and macroscopical evaluation – Pay specific attention to dissect lymph nodes
Collection of non-tumour tissues	– Think well in advance of research questions making the collection worthwhile – Talk to colleagues; there can be huge research potential
Different sample processing protocols for different collaborators	– Facilitate discussions among collaborators to simplify and homogenise the protocols – Make sure collaborators put effort into training the autopsy team for specific protocols
Sample processing is time-consuming	– Divide the work as much as possible – Have multiple people trained for processing – Encourage the pick-up and processing of fresh samples by collaborators themselves – Freeze at autopsy; process later
Challenges related to the set-up of a data management system	
Set-up of a new system or customisation of an existing one	– Comply with biobank requirements from the start – Personnel dedicated to this task should have a scientific and IT background
Logistical challenges related to sample registering/annotation	
Uniform labelling in multicenter studies	– Have specific SOPs per sub-study/cancer type that clearly state labelling instructions
Labelling is time-consuming	– Pre-label samples – Have templates during the tissue donation – Adopt a quick, uniform coding system – Photographic documentation during the autopsy can help to rectify mistakes
Registering sample-specific timepoints	– Time of collection/freezing is the most crucial timepoint – If feasible, set up a system where barcode scanning is linked to timestamping
Challenges related to sample quality	
Fragility of RNA and other molecules	– Start the autopsy as soon as possible – Cool the body as soon as possible after death – For long-duration autopsies, organ cooling can be preferred over body cooling
Assessment of sample quality	– Give feedback to tissue processing members when quality data become available – Implement a waterfall strategy to make sure no resources are wasted (e.g. first confirmation of tumour content before any downstream analyses) – Insist on getting feedback from collaborators on sample quality – Take repeated samples from the same site to assess declines in quality with time – Mimic autopsy procedure on mice harbouring PDXs to assess sample quality with increasing postmortem interval – Document any changes in sample collection/processing strategy very well
Other scientific challenges	
Getting access to historical samples	– Identify clinical/research studies that may store patient samples and collaborate from the start – Actively consult the pathology department
Integrating different analyses performed on the samples	– Centralise standard histological characterisation of samples – Make sure this information is accessible to all team members and collaborators
Getting access to clinical data after death	– In case access to clinical data is lost after death, make sure all relevant information is captured beforehand
Challenges related to the impact of the procedure on the funeral	
Patient/family wishes regarding funeral	– Be transparent about whether any incisions will be visible – Advise providing clothes that cover collarbones and sternum for open coffin viewing – Advise providing a wig or scarf for open coffin viewing if brain was inspected – Minimise incisions in the neck region by dissecting subcutaneous layers neatly upwards – Communicate well with the mortuary (often referred to as morgue in countries other than the UK), transport companies, and funeral homes

CSF, cerebrospinal fluid.

around 3 h (median of reported medians) to complete [range of medians 1 h (Semmelweis University) to 6.5 h (UPTIDER)] (Figure 3A). Several factors influenced autopsy times. Research teams performing the autopsies themselves reported longer autopsy durations compared with clinical pathology services. On-site sample processing prolonged the autopsy; many programmes instead transported samples on ice to a research laboratory. Extensive annotation and electronic registration of sample information added to autopsy times (see 'Sample and data management' below). Lastly, three programmes implemented body sterilisation and the use of sterile drapes to reduce infection risk in subsequent tumour models, potentially slightly increasing autopsy durations.

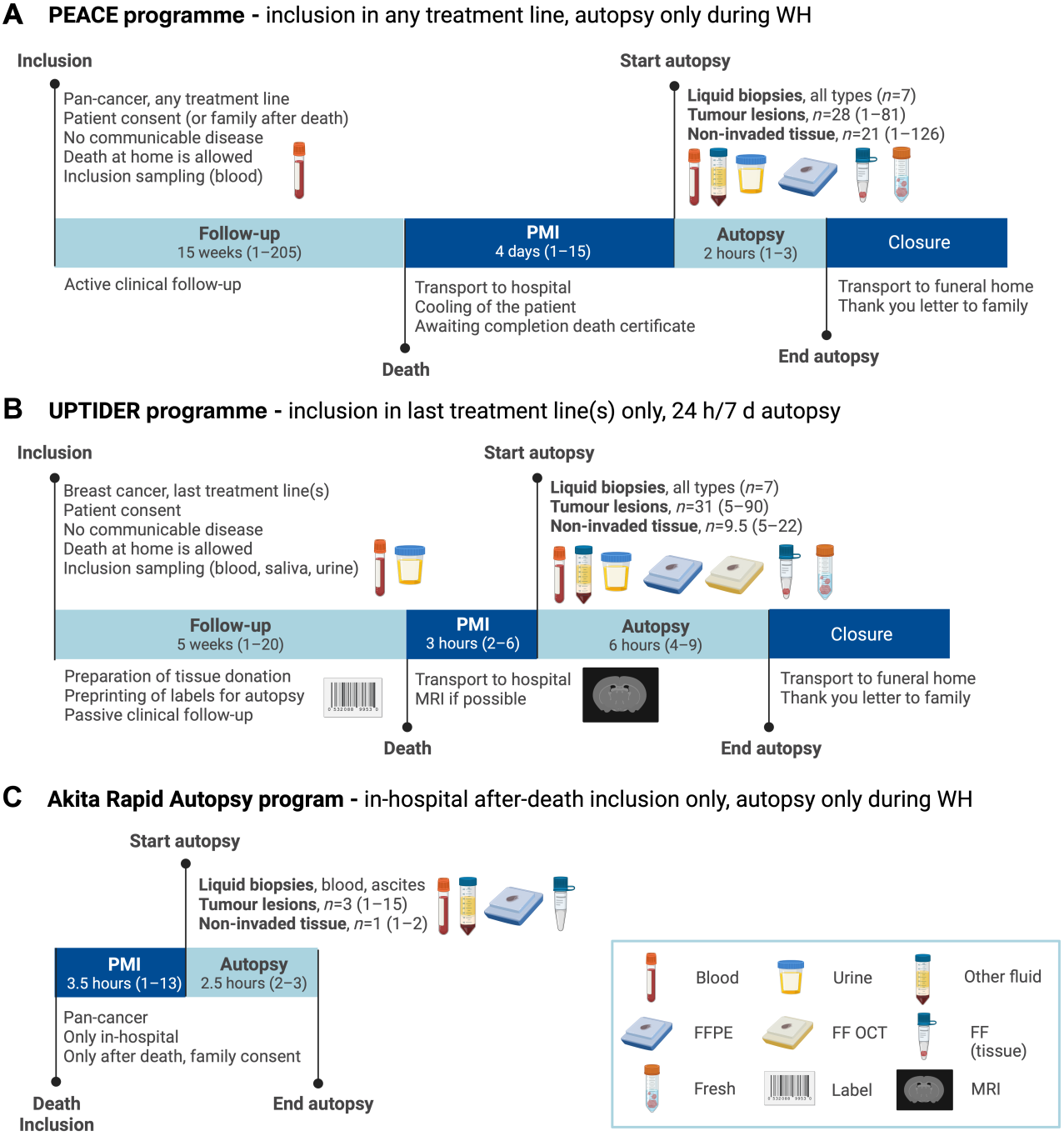

Figure 2. Examples of patient timelines in three different programmes. (A) PEACE programme. (B) UPTIDER programme. (C) Akita Rapid Autopsy Program. Number of liquids represents liquid types (e.g. blood, ascites, …). When 'all types' are mentioned, it means that blood, ascites, bone marrow, pleural fluid, pericardial fluid, cerebrospinal fluid, urine, and possibly vitreous fluid are collected. Other numbers are presented as median (range). PMI, postmortem interval, time between death and start of the autopsy; MRI, magnetic resonance imaging; WH, working hours; FF, fresh (snap) frozen; FFPE, formalin-fixed, paraffin-embedded; FF OCT, fresh frozen in optimal cutting temperature compound. Created with BioRender.com.

Clinical autopsy rooms were usually used and additional equipment was brought in for the procedure. Supplementary material, Figure S2 depicts the room's set-up in two different programmes. Almost all programmes ($n = 11$) collected blood first and all programmes ($n = 14$) collected other types of body fluids, such as ascites, bone marrow, pleural fluid, pericardial fluid, cerebrospinal fluid, urine, vitreous fluid, or aqueous humour (Figure 3D). Next, a patient-specific order of organ inspection was followed in eight programmes, while others stuck to the order in standard clinical autopsies. Photographical documentation of lesions was implemented in 12 programmes. The number of malignant lesions sampled per patient depended on disease burden, tissue viability assessment, and extent of exploration of bone and lymph node metastases. The median number of lesions sampled per patient was 15.5 (median of all medians) and even ≥20 in six

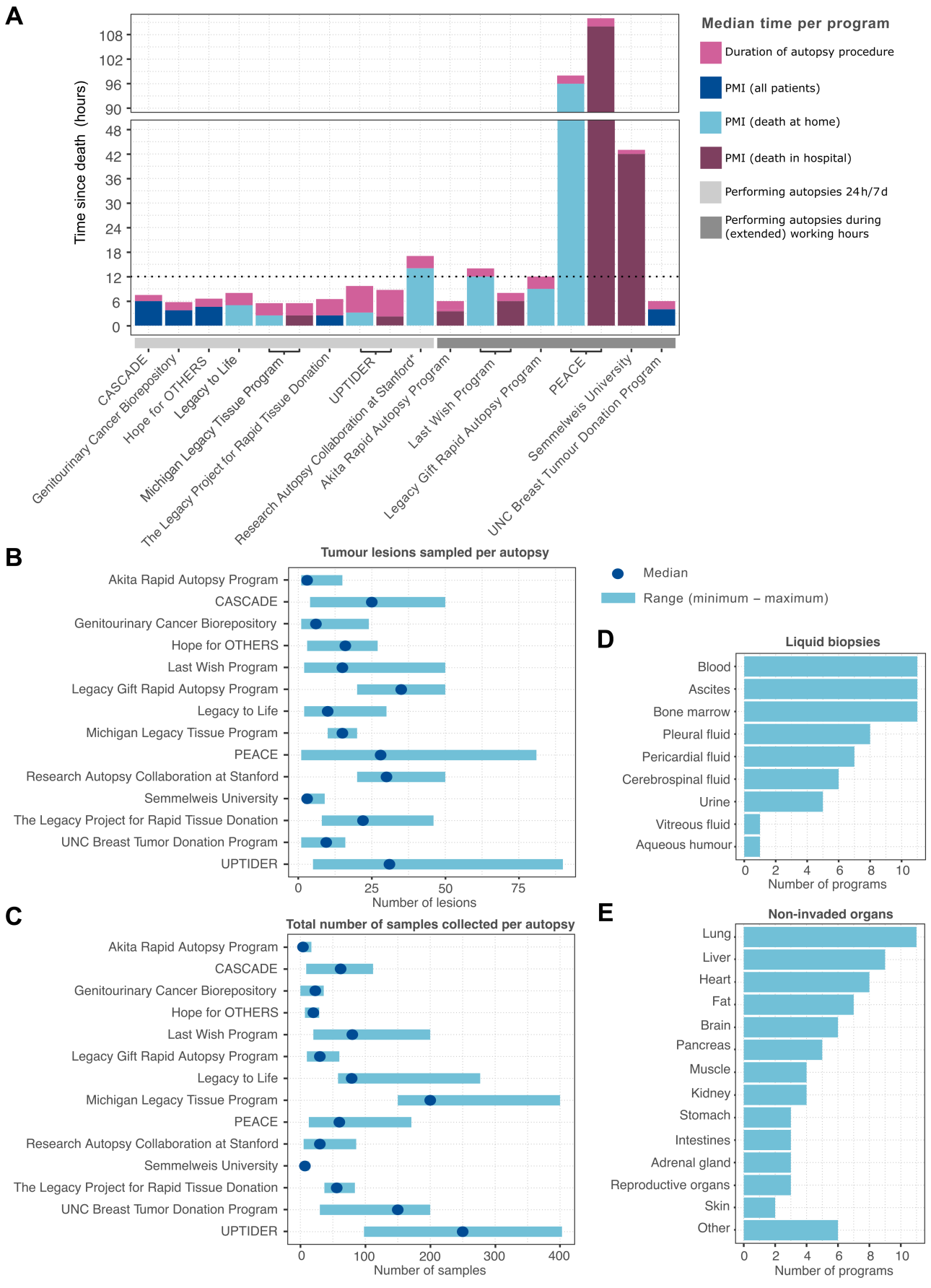

Figure 3 Legend on next page.

programmes (Figure 3B). Many programmes implemented multiregional sampling for large lesions [up to 38 regions for one tumour site (PEACE)]. All but one programme collected both snap-frozen and formalin-fixed samples, sometimes alongside other processing methods (fresh, viably frozen, …). One programme froze any remaining tumour material in vacuum bags. Normal tissue from the same organ with metastases was collected in almost all programmes ($n = 13$). Other non-invaded organ samples were additionally collected in 12 programmes, either as part of the autopsy routine or to answer specific research questions (Figure 3E). The median number of samples collected during each autopsy per patient ranged from 4 (Akita Rapid Autopsy Program) to 250 (UPTIDER), with the median of all medians being 58 (Figure 3C).

Sample and data management

The high number of samples retrieved within a short timeframe demanded an efficient sample registration strategy. Half of the programmes ($n = 7$) created sample labels before autopsy start. Barcoding helped seven programmes to track samples, though only one programme used it at autopsy for registration of sample-specific timepoints and storage locations. Information ultimately recorded for each sample often included the organ (based on anatomical nomenclature or using organ codes [40]) and the exact location of sampling (for correlation with imaging or treatment response [41–43]), alongside the processing method and sample-specific timepoints. While most programmes try to access the tumour samples that were collected during the patient's life, this can be challenging, especially with regard to the primary tumour, which has often been surgically removed in another hospital many years before the autopsy (Table 1).

Capturing comprehensive clinical patient information was equally challenging due to the complex and diverse disease trajectory of metastatic disease. Eight programmes had set up electronic databases, most commonly in RedCap ($n = 5$). Usually, access to the patient's medical file remained available after death for information extraction as research questions evolved.

Other logistical considerations

Most programmes ($n = 11$) purchased equipment specifically for the study including processing equipment, bone drills, logistic equipment, sterilisation equipment, and consumables. Estimating the total price per patient was challenging for five programmes. The Akita Rapid Autopsy Program reported a cost of only USD 20 per patient due to enrolling in-hospital patients only and covering the pathologist's salary through their clinical position. For seven programmes, the price ranged between USD 1,000 and 5,000 per patient; one programme even reported a price range of USD 3,000–10,000. The price was often highly influenced by personnel costs, with some researcher time covered through grants and other personnel requiring full funding. Two programmes reported an autopsy fee of USD 1,500 being charged per patient. Transport of the body either was done in-kind or ranged between USD 185 and 1,500 in median price. Postmortem imaging costs ranged between USD 250 and 750 per patient, or was included in the autopsy fee.

The biggest financial contributors were research foundations [mentioned in nine programmes, median contribution out of total budget 45% (range 5–100%)]. This was followed by funding through the host university [seven programmes, median contribution 50% (range 10–95%)] and the affiliated hospitals [four programmes, median contribution 70% (range 6–100%)]. Three programmes additionally received support through private donors, accounting for 20%, 50%, and 50% of their total budget. Of interest, two programmes implemented cost recovery structures where end users were charged for the samples received (contribution to total budget: 25% and 30%), incentivising them to include cost recovery in grants. Prices varied based on collaboration type (close academic partners versus non-affiliated institutes or industry/commercial partners). No programmes reported structural funding from industry or pharmaceutical companies.

Research opportunities and achievements

Postmortem programmes allow high-volume sample collection of tumour tissue, non-tumour tissue, and liquid biopsies, sometimes in combination with longitudinal sampling (the original primary tumour and/or metastases during life) (Figure 4A). This has already enabled high-impact research, as highlighted in Figure 4B and Table 2 with examples from the 14 programmes. Genomics, particularly sequencing multiple metastases per patient, has revealed insights into metastatic seeding, driver events,

Figure 3. Key autopsy figures for the programmes included in this study. (A) Median time between death and start of the autopsy (PMI, postmortem interval) for each programme. Dark blue: median for all patients in the programme (irrespective of place of death); light blue: median for patients in the programme dying at home; dark purple: median for patients dying in the hospital. Median duration of all autopsies in the programme added on top in pink. *The Stanford University programme has recently moved to 24 h/7 day autopsies; the figures presented are from before that time. (B) Number of tumour lesions sampled per autopsy in each programme. Light blue bar presents range (minimum to maximum number per patient); dark blue dot indicates the median per patient. (C) Total number of solid samples collected per autopsy in each programme (tumour samples as well as non-tumour samples). Light blue bar presents total range (minimum to maximum number per patient); dark blue dot indicates the median per patient. (D) Number of programmes collecting different types of liquid biopsies during the autopsy. The aqueous humour is from the anterior eye. (E) Number of programmes routinely collecting samples from different non-invaded organs during the autopsy. On top of this, many programmes take non-tumour samples from the organs where a metastasis is found ('adjacent normal'). Other: bone, pituitary gland, spleen, nails, thyroid.

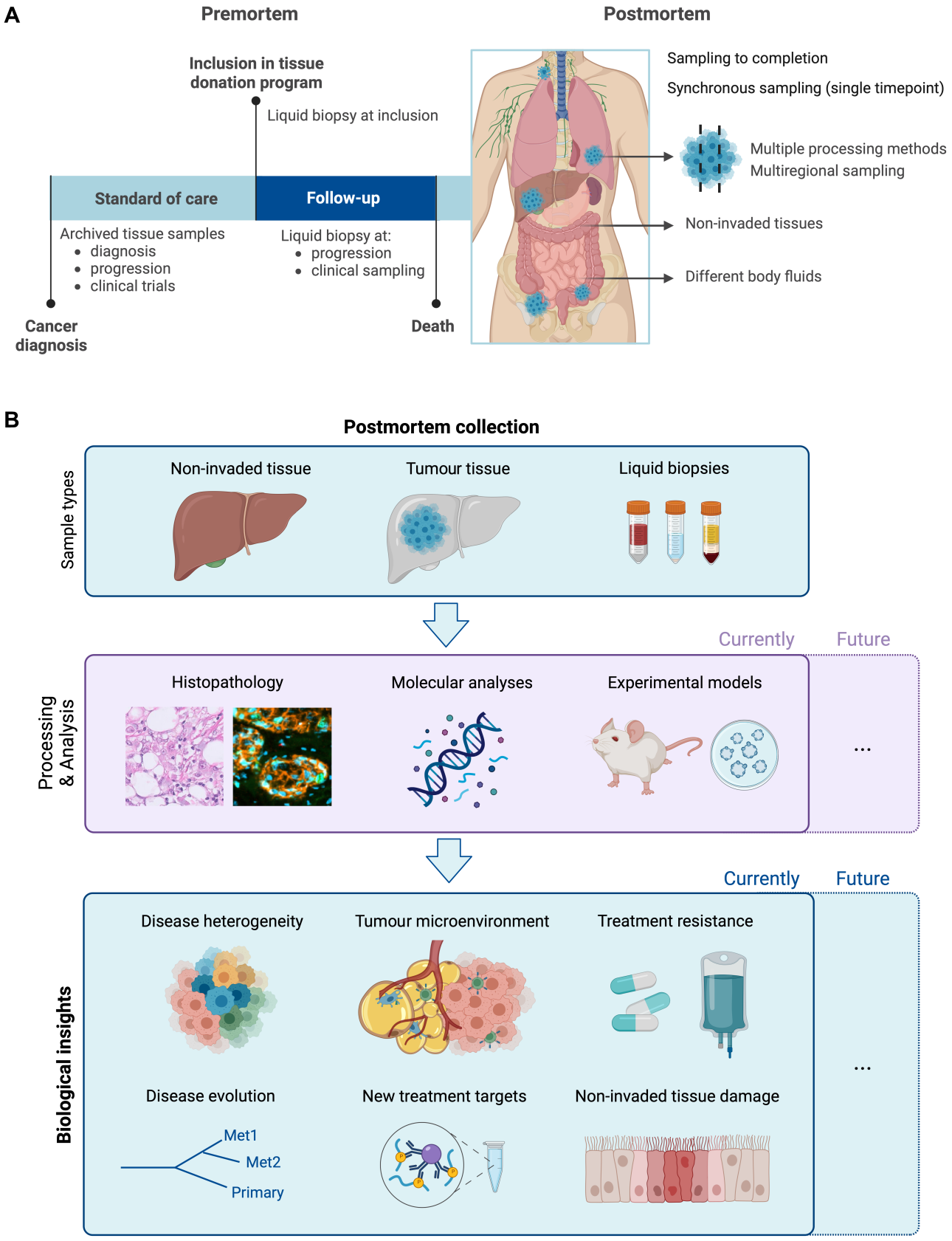

Figure 4. Opportunities of tissue donation programmes. (A) Opportunities for sample collection in the context of rapid autopsy programmes. Tissue samples requested from clinical and study archives and liquid biopsies collected specifically for the programme can form a biorepository of premortem (longitudinal) samples. At autopsy, the sample collection opportunities are virtually unlimited, and include extensive tumour and liquid biopsy sampling as well as the collection of non-tumour tissues for specific research questions. (B) Opportunities for understanding metastatic cancer through research autopsies. Created with Biorender.com.

Table 2. Research opportunities and achievements. Examples from programmes included in this article are given for each category.

Intra-patient inter-lesion heterogeneity in genomic and phenotypic characteristics
Wide intra-patient inter-lesion variety in percentage of cells expressing prostate-specific antigen (PSA) or neuro-endocrine features in metastatic prostate cancer [11]
Heterogeneity in expression of hormone receptor and other therapeutic targets between primaries and matched metastases in breast cancer. Methylation of assessed promotor regions was more similar [68]
Limited heterogeneity in driver events, copy number profile, cell cycle activity, and androgen receptor activity between metastases within one patient with prostate cancer [44]
Important heterogeneity in subclonal structure between primary and metastatic disease in breast cancer. Treatment drives genomic subclonal heterogeneity [15]
Analysis of multiple metastases per patient allowed the evaluation of intra-patient heterogeneity in the presence of specific gene fusion events in breast cancer [45]
Multiple subclones with a variety of mechanisms of therapeutic resistance can co-exist in one patient with ovarian cancer [46]
Intra-patient inter-metastasis heterogeneity of HER2-low status complicates its assessment on one biopsy in metastatic breast cancer [69]
Characterisation and evaluation of distribution of polypoid giant cancer cells in metastatic castration-resistant prostate cancer [72]
Intra-patient inter-lesion heterogeneity in phenotype was observed in metastatic prostate cancer, including differences in androgen receptor expression and PSA expression [70]
DNA methylation changes are very similar between metastases within patients with prostate cancer. Regions with consistent methylation show enrichment for cancer-related genes [47]
Metastatic lesions within patients and between patients with urothelial carcinoma shared actionable mutations [48]
Many of the genetic changes conferring treatment resistance were shared between metastases in the same patient with melanoma [49]
No correlation between ERG and expression of PSA or androgen receptor in individual metastases in prostate cancer [71]
Prognostic and predictive biomarker expression differs between primary breast cancer and matched metastases and might depend on the organ of metastasis. Immune profiles were heterogeneous too [77]
Characterisation and comparison of non-ossified bone metastases to non-osseous metastases from the same prostate cancer patients [78]
Immune activation varies by organ site of involvement in metastatic breast cancer [79]
Multi-omic analyses on primary breast tumours versus during-life (mostly liver) and after-death (many other soft tissues) metastases reveal events that may explain metastatic tumour behaviours [79]
Mechanisms of metastatic evolution and spread, including phylogenetic reconstruction
Almost all targetable drivers in metastases in patients with breast cancer are already present in the primary tumour. Multiclonal seeding is often seen [50]
Two possible scenarios of dissemination patterns of breast cancer (monoclonal and multiclonal) are observed, as well as cross-seeding between metastases [51]
While some patients with metastatic breast cancer presented with predominantly monoclonal seeding patterns, others showed predominantly multiclonal seeding [52]
Clonal dynamics as assessed on multiple metastases at autopsy confirms different modes of metastatic dissemination in clear-cell renal cell carcinoma [53]
Phylogenetic trees in metastatic pancreatic cancer show organ-specific branches [54]
Copy number and cell ploidy changes drive evolution to end-stage disease in melanoma (compared with SNVs driving transformation in early disease) [55]
Most genetic drivers in metastases in breast cancer were already established in the primary tumour. Drivers unique to metastases were mutations in hormone receptors. Most driver events were copy number changes. Multiclonal seeding was frequent [56]
Incidence of germline mutations in genes mediating DNA-repair processes among men with metastatic prostate cancer was significantly higher than the incidence among men with localised prostate cancer [57]
Mechanisms behind genomic instability in pancreatic cancer include rearrangements disrupting telomere function and cell cycle control [54]
Distinct genotypes in end-stage pancreatic cancer correlate with the pattern of clinical organ failure (metastatic versus locally destructive disease) [66]
Monoclonal seeding is the dominant pattern in metastatic prostate cancer [58]
Genetic profiles of metastases reflect the profile of the primary in pancreatic cancer. Time between occurrence of the initiating mutation and the acquisition of metastatic ability was calculated to be at least 5 years [59]
Mutations in driver genes were similar across metastases within each patient with pancreatic cancer [60]
Upper tract metastatic urothelial carcinoma has lower overall mutational burden but higher structural variability compared with lower tract urothelial carcinoma [48]
Low overall mutation rates were observed in metastatic end-stage prostate cancer [61]
Difference in prevalence of certain driver mutations in metastatic disease compared with reported prevalence in primary pancreatic cancer [62]
Unique insight into prostate cancer clonality and spread [80]
Patterns of metastatic spread
The pattern of metastasis observed at autopsy showed visceral involvement to be more common than generally thought in metastatic prostate cancer [70]
Patterns of metastatic disease differ between patients with breast and ovarian cancer who are *BRCA1/2* carriers and those who are non-carriers, suggesting different mechanisms of dissemination [73]
Evaluation of mechanisms of treatment resistance/response
Association between certain genomic alterations and treatment response in metastatic prostate cancer, such as longer responses to carboplatin in patients with defects in DNA-repair proteins [44]
ESR1 fusion enrichment may represent secondary resistance to more aggressive endocrine therapies in breast cancer [63]
New genomic mechanisms of disruption of androgen receptor signalling identified in metastatic prostate cancer [61]
Convergent loss of *PTEN* is a mechanism of resistance to PI3K inhibition in breast cancer [64]
Mechanisms of resistance to immunotherapy in melanoma [81]
Different types of reversion mutations found in the *BRCA2* gene in patients with ovarian cancer, representing a mechanism of resistance to PARP inhibition [65]

(Continues)

Evaluation of non-tumour tissue samples
EGFR driver mutations were found in non-cancerous lung samples retrieved at autopsy, highlighting the presence of pre-existing mutant cells possibly susceptible to pollution-associated tumour promotion [76]
Potential of liquid biopsies and blood-based analyses
Circulating tumour DNA could be detected in blood collected postmortem in patients with prostate cancer and allowed identification of mutations present in different metastases [67]
Analysis of T-cell repertoires across multiple tumour lesions as well as in circulation in a patient with renal cell carcinoma highlights pitfalls in interpreting T-cell cross-reactivity between tumours and immune checkpoint inhibitor immune-related adverse events based on profiles in peripheral blood or one sample only [82]
Tumour model development
Patient-derived xenografts established from two postmortem metastases allowed the evaluation of the role of androgen receptor splice variant-7 in treatment resistance and tumour evolution in prostate cancer [74]
Successfully established patient-derived xenografts from postmortem samples allowed the investigation of candidate therapies in castration-resistant prostate cancer to prioritise treatments for clinical translation [75]

treatment resistance, and disease phylogenetics [15,44–66]. Additionally, it has allowed the exploration of the use of liquid biopsies to profile the different metastases [67]. Phenotyping has highlighted heterogeneity in clinically used biomarkers and the inadequacy of a single biopsy to assess treatment eligibility [11,68–72]. Autopsy programmes have comprehensively assessed metastatic organ involvement [70,73] and have facilitated the establishment of patient-derived xenografts (PDXs) and other experimental models with subsequent investigation of treatment sensitivity [74,75]. Some programmes are additionally exploring new treatment targets, the metastatic tumour micro-environment, and the correlation between histological and imaging features. Non-tumour tissue research has so far explored the presence of driver events in non-cancerous tissue [76]. Other promising avenues on these tissues include assessment of treatment toxicity, paraneoplastic effects, pre-metastatic niches, and tumour dormancy. Additionally, non-cancer-related health research can also be conducted on these tissues; for example, non-tumour brain samples collected in the UPTIDER programme are used for research on neurodegenerative diseases.

Discussion

We present here the shared experience and accomplishments of 14 research autopsy programmes that were created to advance metastatic cancer research around the world. At the geographical level, most programmes are in the United States and we could not identify any programme in South America or Africa. This means that, currently, these programmes might not be capturing the full spectrum of the disease.

The programmes ranged from slight modification of clinical autopsy procedures to extensive postmortem tissue sampling performed by research personnel. Autopsies performed 24 h/7 days had a median PMI of only 4 h, enabling the qualitative collection of fragile molecules and viable cells. This structure, however, came at a psychological and logistical cost. All programmes have successfully collected highly valuable liquid and tissue samples, with a median of 58 samples stored per patient across all programmes, including from organs otherwise unethical/impossible to sample. The rapid nature of the procedures (often completed within 12 h after death) and implementation of cooling mitigated postmortem effects on molecules/RNA degradation. Genomic analyses were possible in every programme, leading to major discoveries in metastatic tumour progression and biology. Sample prioritisation, sterile procurement, and reduced transport times have facilitated the creation of unique tumour models shaping future drug discoveries and testing.

In the era of precision medicine, autopsy programmes can be an invaluable link in the research chain towards better patient outcomes. Through this work, we hope to foster collaborations (contact details are provided in supplementary material, Table S2 for all programmes) and to encourage the creation of new programmes. A society of research autopsy programmes will help to achieve this goal and is currently being created, including non-oncological and paediatric programmes. Importantly, we also plan on further exploring how the role of patients in the design and support of the programmes can be increased in the future, as they are the cornerstone of and the sole reason for the research we do.

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Author contributions statement

TG was responsible for conceptualisation, methodology, validation, formal analysis, investigation, resources, data curation, writing the original draft, review and editing of the manuscript, visualisation and project administration. MM was responsible for conceptualisation, methodology, review and editing of the manuscript and project administration. JEH was responsible for resources, review and editing of the manuscript and supervision. SO, AVL, WVDB and GF were responsible for methodology, resources, and review and editing of the manuscript. LM, JMA, MR, SP, HT, LD, DB, ERB, KI, MS, LR, ALW, LG, RMu, PC, AK, CN-L, HB, CS, MJ-H, LK, CM, MC, AMC, AW, RMe, ZR, LAC, EK, DM, AG, JK, MS, BS and A-MT helped with resources and writing the manuscript (review and editing). CD was involved in conceptualisation, methodology, review and editing of the manuscript and supervision.

Data availability statement

To avoid misinterpretation, the filled-out fact sheets of individual programmes will not be shared. However, programmes agreeing to be contacted for further information have their details listed in supplementary material, Table S2.

References

1. Sung H, Ferlay J, Siegel RL, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; **71:** 209–249.
2. Lambert AW, Pattabiraman DR, Weinberg RA. Emerging biological principles of metastasis. *Cell* 2017; **168:** 670–691.
3. Dujon AM, Capp JP, Brown JS, *et al*. Is there one key step in the metastatic cascade? *Cancers (Basel)* 2021; **13:** 3693.
4. Ganesh K, Massagué J. Targeting metastatic cancer. *Nat Med* 2021; **27:** 34–44.
5. Gerstberger S, Jiang Q, Ganesh K. Metastasis. *Cell* 2023; **186:** 1564–1579.
6. McGranahan N, Swanton C. Clonal heterogeneity and tumor evolution: past, present, and the future. *Cell* 2017; **168:** 613–628.
7. Martínez-Reyes I, Chandel NS. Cancer metabolism: looking forward. *Nat Rev Cancer* 2021; **21:** 669–680.
8. Knoche SM, Larson AC, Sliker BH, *et al*. The role of tumor heterogeneity in immune–tumor interactions. *Cancer Metastasis Rev* 2021; **40:** 377–389.
9. Lawson DA, Kessenbrock K, Davis RT, *et al*. Tumour heterogeneity and metastasis at single-cell resolution. *Nat Cell Biol* 2018; **20:** 1349–1360.
10. Lenz G, Onzi GR, Lenz LS, *et al*. The origins of phenotypic heterogeneity in cancer. *Cancer Res* 2022; **82:** 3–11.
11. Roudier MP, True LD, Higano CS, *et al*. Phenotypic heterogeneity of end-stage prostate carcinoma metastatic to bone. *Hum Pathol* 2003; **34:** 646–653.
12. Marusyk A, Janiszewska M, Polyak K. Intratumor heterogeneity: the Rosetta Stone of therapy resistance. *Cancer Cell* 2020; **37:** 471–484.
13. Pereira B, Chen CT, Goyal L, *et al*. Cell-free DNA captures tumor heterogeneity and driver alterations in rapid autopsies with pre-treated metastatic cancer. *Nat Commun* 2021; **12:** 3199.
14. Cresswell GD, Nichol D, Spiteri I, *et al*. Mapping the breast cancer metastatic cascade onto ctDNA using genetic and epigenetic clonal tracking. *Nat Commun* 2020; **11:** 1446.

15. Savas P, Teo ZL, Lefevre C, *et al*. The subclonal architecture of metastatic breast cancer: results from a prospective community-based rapid autopsy program "CASCADE". *PLoS Med* 2016; **13:** e1002204.
16. Iacobuzio-Donahue CA, Michael C, Baez P, *et al*. Cancer biology as revealed by the research autopsy. *Nat Rev Cancer* 2019; **29:** 686–697.
17. Duregon E, Schneider J, DeMarzo AM, *et al*. Rapid research autopsy is a stealthy but growing contributor to cancer research. *Cancer* 2019; **125:** 2915–2919.
18. Dankner M, Issa-Chergui B, Bouganim N. Post-mortem tissue donation programs as platforms to accelerate cancer research. *J Pathol Clin Res* 2020; **6:** 163–170.
19. Hooper JE. Rapid autopsy programs and research support: the pre- and post-COVID-19 environments. *AJSP Rev Rep* 2021; **26:** 100–107.
20. Robb TJ, Tse R, Blenkiron C. Reviving the autopsy for modern cancer evolution research. *Cancers (Basel)* 2021; **13:** 409.
21. Dutta R, Mahajan KR, Nakamura K, *et al*. Comprehensive autopsy program for individuals with multiple sclerosis. *J Vis Exp* 2019. doi: 10.3791/59511
22. Trujillo Diaz D, Hernandez NC, Cortes EP, *et al*. Banking brains: a pre-mortem "how to" guide to successful donation. *Cell Tissue Bank* 2018; **19:** 473–488.
23. Mez J, Daneshvar DH, Kiernan PT, *et al*. Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. *JAMA* 2017; **318:** 360–370.
24. Kretzschmar H. Brain banking: opportunities, challenges and meaning for the future. *Nat Rev Neurosci* 2009; **10:** 70–78.
25. Jonkman LE, de Graaf YG, Bulk M, *et al*. Normal Aging Brain Collection Amsterdam (NABCA): a comprehensive collection of postmortem high-field imaging, neuropathological and morphometric datasets of non-neurological controls. *Neuroimage Clin* 2019; **22:** 101698.
26. De Cock KM, Zielinski-Gutiérrez E, Lucas SB. Learning from the dead. *N Engl J Med* 2019; **381:** 1889–1891.
27. Rawlings SA, Layman L, Smith D, *et al*. Performing rapid autopsy for the interrogation of HIV reservoirs. *AIDS* 2020; **34:** 1089–1092.
28. Layne SP, Walters KA, Kash JC, *et al*. More autopsy studies are needed to understand the pathogenesis of severe COVID-19. *Nat Med* 2022; **28:** 427–428.
29. McGuone D, Sinard J, Gill JR, *et al*. Autopsy services and emergency preparedness of a tertiary academic hospital mortuary for the COVID-19 public health emergency: the Yale plan. *Adv Anat Pathol* 2020; **27:** 355–362.
30. Carpenito L, D'Ercole M, Porta F, *et al*. The autopsy at the time of SARS-CoV-2: protocol and lessons. *Ann Diagn Pathol* 2020; **48:** 151562.
31. Bavi P, Siva M, Abi-Saab T, *et al*. Developing a pan-cancer research autopsy programme. *J Clin Pathol* 2019; **72:** 689–695.
32. Alsop K, Thorne H, Sandhu S, *et al*. A community-based model of rapid autopsy in end-stage cancer patients. *Nat Biotechnol* 2016; **34:** 1010–1014.
33. Rubin MA, Putzi M, Mucci N, *et al*. Rapid ('warm') autopsy study for procurement of metastatic prostate cancer. *Clin Cancer Res* 2000; **6:** 1038–1045.
34. Rosenzweig M, Miller LA, Lee AV, *et al*. The development and implementation of an autopsy/tissue donation for breast cancer research. *New Bioeth* 2021; **27:** 349–361.
35. Pisapia DJ, Salvatore S, Pauli C, *et al*. Next-generation rapid autopsies enable tumor evolution tracking and generation of preclinical models. *JCO Precis Oncol* 2017; 1: PO.16.00038.
36. Kambhampati M, Perez JP, Yadavilli S, *et al*. A standardized autopsy procurement allows for the comprehensive study of DIPG biology. *Oncotarget* 2015; **6:** 12740–12747.
37. Broniscer A, Baker JN, Baker SJ, *et al*. Prospective collection of tissue samples at autopsy in children with diffuse intrinsic pontine glioma. *Cancer* 2010; **116:** 4632–4637.
38. Bacon ER, Ihle K, Lee PP, *et al*. Building a rapid autopsy program – a step-by-step logistics guide. *Transl Med Commun* 2020; **5:** 1–14.
39. Achkar T, Wilson J, Simon J, *et al*. Metastatic breast cancer patients: attitudes toward tissue donation for rapid autopsy. *Breast Cancer Res Treat* 2016; **155:** 159–164.
40. SEER ICD-O-3 Coding Materials. [Accessed 29 May 2023]. Available from: https://seer.cancer.gov/icd-o-3/.
41. Rusch VW, Asamura H, Watanabe H, *et al*. The IASLC Lung Cancer Staging Project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2009; **4:** 568–577.
42. Robbins KT, Shaha AR, Medina JE, *et al*. Consensus statement on the classification and terminology of neck dissection. *Arch Otolaryngol Head Neck Surg* 2008; **134:** 536–538.
43. Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. *J Hepatobiliary Pancreat Surg* 2005; **12:** 351–355.
44. Kumar A, Coleman I, Morrissey C, *et al*. Substantial interindividual and limited intraindividual genomic diversity among tumors from men with metastatic prostate cancer. *Nat Med* 2016; **22:** 369–378.
45. Christie EL, Pattnaik S, Beach J, *et al*. Multiple ABCB1 transcriptional fusions in drug resistant high-grade serous ovarian and breast cancer. *Nat Commun* 2019; **10:** 1295.
46. Burdett NL, Willis MO, Alsop K, *et al*. Multiomic analysis of homologous recombination-deficient end-stage high-grade serous ovarian cancer. *Nat Genet* 2023; **55:** 437–450.
47. Aryee MJ, Liu W, Engelmann JC, *et al*. DNA methylation alterations exhibit intraindividual stability and interindividual heterogeneity in prostate cancer metastases. *Sci Transl Med* 2013; **5:** 169ra10.
48. Winters BR, De Sarkar N, Arora S, *et al*. Genomic distinctions between metastatic lower and upper tract urothelial carcinoma revealed through rapid autopsy. *JCI Insight* 2019; **5:** e128728.
49. Makohon-Moore AP, Lipson EJ, Hooper JE, *et al*. The genetic evolution of treatment-resistant cutaneous, acral, and uveal melanomas. *Clin Cancer Res* 2021; **27:** 1516–1525.
50. Hoadley KA, Siegel MB, Kanchi KL, *et al*. Tumor evolution in two patients with basal-like breast cancer: a retrospective genomics study of multiple metastases. *PLoS Med* 2016; **13:** e1002174.
51. Brown D, Smeets D, Székely B, *et al*. Phylogenetic analysis of metastatic progression in breast cancer using somatic mutations and copy number aberrations. *Nat Commun* 2017; **8:** 14944.
52. Avigdor BE, Cimino-Mathews A, DeMarzo AM, *et al*. Mutational profiles of breast cancer metastases from a rapid autopsy series reveal multiple evolutionary trajectories. *JCI Insight* 2017; **2:** e96896.
53. Turajlic S, Xu H, Litchfield K, *et al*. Tracking cancer evolution reveals constrained routes to metastases: TRACERx Renal. *Cell* 2018; **173:** 581–594.e12.
54. Campbell PJ, Yachida S, Mudie LJ, *et al*. The patterns and dynamics of genomic instability in metastatic pancreatic cancer. *Nature* 2010; **467:** 1109–1113.
55. Vergara IA, Mintoff CP, Sandhu S, *et al*. Evolution of late-stage metastatic melanoma is dominated by aneuploidy and whole genome doubling. *Nat Commun* 2021; **12:** 1434.
56. Siegel MB, He X, Hoadley KA, *et al*. Integrated RNA and DNA sequencing reveals early drivers of metastatic breast cancer. *J Clin Invest* 2018; **128:** 1371–1383.
57. Pritchard CC, Mateo J, Walsh MF, *et al*. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. *N Engl J Med* 2016; **375:** 443–453.
58. Liu W, Laitinen S, Khan S, *et al*. Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer. *Nat Med* 2009; **15:** 559–565.
59. Yachida S, Jones S, Bozic I, *et al*. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. *Nature* 2010; **467:** 1114–1117.

60. Makohon-Moore AP, Zhang M, Reiter JG, *et al*. Limited heterogeneity of known driver gene mutations among the metastases of individual patients with pancreatic cancer. *Nat Genet* 2017; **49:** 358–366.
61. Grasso CS, Wu YM, Robinson DR, *et al*. The mutational landscape of lethal castration-resistant prostate cancer. *Nature* 2012; **487:** 239–243.
62. Embuscado EE, Laheru D, Ricci F, *et al*. Immortalizing the complexity of cancer metastasis: genetic features of lethal metastatic pancreatic cancer obtained from rapid autopsy. *Cancer Biol Ther* 2005; **4:** 548–554.
63. Hartmaier RJ, Trabucco SE, Priedigkeit N, *et al*. Recurrent hyperactive ESR1 fusion proteins in endocrine therapy-resistant breast cancer. *Ann Oncol* 2018; **29:** 872–880.
64. Juric D, Castel P, Griffith M, *et al*. Convergent loss of PTEN leads to clinical resistance to a PI(3)Kα inhibitor. *Nature* 2015; **518:** 240–244.
65. Patch AM, Christie EL, Etemadmoghadam D, *et al*. Whole-genome characterization of chemoresistant ovarian cancer. *Nature* 2015; **521:** 489–494.
66. Iacobuzio-Donahue CA, Fu B, Yachida S, *et al*. *DPC4* gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. *J Clin Oncol* 2009; **27:** 1806–1813.
67. Takai E, Maeda D, Li Z, *et al*. Post-mortem plasma cell-free DNA sequencing: proof-of-concept study for the "liquid autopsy". *Sci Rep* 2020; **10:** 2120.
68. Wu JM, Fackler MJ, Halushka MK, *et al*. Heterogeneity of breast cancer metastases: comparison of therapeutic target expression and promoter methylation between primary tumors and their multifocal metastases. *Clin Cancer Res* 2008; **14:** 1938–1946.
69. Geukens T, De Schepper M, Richard F, *et al*. Intra-patient and inter-metastasis heterogeneity of HER2-low status in metastatic breast cancer. *Eur J Cancer* 2023; **188:** 152–160.
70. Shah RB, Mehra R, Chinnaiyan AM, *et al*. Androgen-independent prostate cancer is a heterogeneous group of diseases: lessons from a rapid autopsy program. *Cancer Res* 2004; **64:** 9209–9216.
71. Udager AM, Shi Y, Tomlins SA, *et al*. Frequent discordance between *ERG* gene rearrangement and ERG protein expression in a rapid autopsy cohort of patients with lethal, metastatic, castration-resistant prostate cancer. *Prostate* 2014; **74:** 1199–1208.
72. Mannan R, Wang X, Bawa PS, *et al*. Polypoidal giant cancer cells in metastatic castration-resistant prostate cancer: observations from the Michigan Legacy Tissue Program. *Med Oncol* 2020; **37:** 16.
73. Thorne H, Devereux L, Li J, *et al*. *BRCA1* and *BRCA2* carriers with breast, ovarian and prostate cancer demonstrate a different pattern of metastatic disease compared with non-carriers: results from a rapid autopsy programme. *Histopathology* 2023; **83:** 91–103.
74. Zhu Y, Dalrymple SL, Coleman I, *et al*. Role of androgen receptor splice variant-7 (AR-V7) in prostate cancer resistance to 2nd-generation androgen receptor signaling inhibitors. *Oncogene* 2020; **39:** 6935–6949.
75. Lawrence MG, Obinata D, Sandhu S, *et al*. Patient-derived models of abiraterone- and enzalutamide-resistant prostate cancer reveal sensitivity to ribosome-directed therapy. *Eur Urol* 2018; **74:** 562–572.
76. Hill W, Lim EL, Weeden CE, *et al*. Lung adenocarcinoma promotion by air pollutants. *Nature* 2023; **616:** 159–167.
77. Szekely B, Nagy ZI, Farago Z, *et al*. Comparison of immunophenotypes of primary breast carcinomas and multiple corresponding distant metastases: an autopsy study of 25 patients. *Clin Exp Metastasis* 2017; **34:** 103–113.
78. Mehra R, Kumar-Sinha C, Shankar S, *et al*. Characterization of bone metastases from rapid autopsies of prostate cancer patients. *Clin Cancer Res* 2011; **17:** 3924–3932.
79. Garcia-Recio S, Hinoue T, Wheeler GL, *et al*. Multiomics in primary and metastatic breast tumors from the AURORA US network finds microenvironment and epigenetic drivers of metastasis. *Nat Cancer* 2023; **4:** 128–147.
80. Mehra R, Tomlins SA, Yu J, *et al*. Characterization of *TMPRSS2*-ETS gene aberrations in androgen-independent metastatic prostate cancer. *Cancer Res* 2008; **68:** 3584–3590.
81. Spain L, Coulton A, Lobon I, *et al*. Late-stage metastatic melanoma emerges through a diversity of evolutionary pathways. *Cancer Discov* 2023; **13:** 1364–1385.
82. Cottrell T, Zhang J, Zhang B, *et al*. Evaluating T-cell cross-reactivity between tumors and immune-related adverse events with TCR sequencing: pitfalls in interpretations of functional relevance. *J Immunother Cancer* 2021; **9:** e002642.

SUPPLEMENTARY MATERIAL ONLINE

Figure S1. Flow diagram of the number of rapid autopsy programmes identified, contacted, and finally included in the survey

Figure S2. Examples of the set-up of the autopsy room in two different programmes

Table S1. Blank version of the five fact sheets containing all questions in the survey

Table S2. Main characteristics of the respective programmes