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文献导读

本期的文献导读是一篇专家综述《漫谈生物样品库》。生物样品库和液体活检领域是相辅相成的。现代医学的核心思想是循证医学，是靠数据支撑的。越是创新的技术，越是需要大量数据的支撑。液体活检是一门被创新所推动的技术，所以对生物样品库的需求也非常明显。在液体活检技术的研发或者使用过程中，尤其是二代测序技术的应用，产生了大量的信息。这些信息需要和过去的、未来的同类信息比对，获得验证或者修正，所以这些信息无疑需要进入某种生物样品库，生物样品库成为液体活检的延伸。另一方面，生物样品库在生物标记物和个体化医疗和等方面的进步，又推动了液体活检在概念和实践方面的进展。目前，生物样品库实际上包含三个层次的内容：（1）实体的生物学样品；（2）相关的分析诊断信息；（3）相关的伦理和法律信息。这其中的伦理和法律方面，提供了生物样品库所面临的最大的挑战。目前在在美国和欧洲这样的生物样品库发达的地区，生物样品库还是鲜为人知的专业概念。在中国的生物样品库，尽管有着世界上最大的潜在患者群和样品来源，还处于初始阶段。随着法律和法规的完善，我们期待生物样品库能够成为一个独立盈利的产业，成为一个和生物信息和诊断行业匹配的新产业。

作者介绍：

李小林

北京大学生物化学学士，杜克大学生物化学博士、博士后。多年从事生物技术的研发、推广、技术以及商务合作。现任美国 GIMDX 公司的市场和技术总监，兼任阳普医疗标本处理系统产品线首席科学家。

邮件：jli@gimdx.com；**联系地址：**GIMDx Inc., Faraday Avenue, Carlsbad, CA 92008, USA.

漫谈生物样品库

生物样品库（Biobanks）是在最近 30 年内兴起的一项生物科技产业，在 2009 年被时代杂志称为影响世界的十大想法之一[1]。生物样品库专注于各项生物医学样品的收集、储存和共享，对于现代生物医学的科研、诊断和治疗方面，都有积极的推动作用。

和液体活检这个井喷式的朝阳产业相比，生物样品库起步更早但是发展平缓， 最近的统计表明， 即使在美国和欧洲这样的生物样品库发达的地区，生物样品库也是鲜为人知的专业概念，在中国就更是不为人知了。为此，我们在本期的《医学拾萃》里专门介绍一下生物样品库。

生物样品库和我们所积极关注的液体活检，是两个相互独立、相互作用的产业，一方面液体活检的样品，无论在检测前或是检测后，都有越发增加的需求需要进入生物样品库，生物样品库成为液体活检的延伸。另一方面，生物样品库在生物标记物和个体化医疗等方面的进步，又推动了液体活检在概念和实践方面的进展。而生物样品库所面临的挑战，无论是管理、经济、伦理、法律，还是其他方面，都直接或间接地影响到液体活检行业。

生物样品库的概念和渊源

现代医学的核心思想是循证医学（evidence-based medicine），又称实证医学，就是统一利用科学方法获取证据，来确认诊断和医疗的成效。循证医学所追溯的这些证据，包括早期的病理学样品为主的组织样本和近年来针对分子诊断技术的更为精细划分的血细胞、核酸等样本，构成了循证医学的基石。我们这些在 IVD 行业的从业人员，包括我们研发、推广仪器、试剂和耗材的同事们，都是服务于医学证据并且依靠这些医学证据来吃饭的。而这些医学证据的汇总，就构成了各类生物样品库[2-9]。

一般来说，生物样品库包含这些三类内容：

第一类：实体部分，是来自人体的生物学样品；

第二类：来自第一类内容的相关信息，包括诊断和分析结果；

第三类：和前两类内容相关的伦理、法律信息。

其中的第一类，即来自人体的生物学样品，是生物样品库的实体部分，它包括全血、血浆、血清、红细胞、白细胞、样签刮取物、DNA、RNA、蛋白质、细胞系、尿液、脑脊髓液、关节润滑液、羊水、血沉棕黄层、骨髓干细胞、组织样品等。在目前情况下，储存量最大、最常用的样品是组织样品，即固定包埋或者冷冻保存的组织样品。这是组织活检的产物，在传统操作里这些组织也是要求保留的，所以有着天然的存量。在近年发展最快的应该是血液样品，包括以上所提到的全血、血细胞和提取物，这是液体活检的产物。

生物样品库的现状和种类

生物样品库的现状可以这样来概况：多种门类，亟待协调，发展迅速，面临挑战。生物样品库不是一家或者一种机构，而是上百种机构。

生物样品库的门类和形式是非常多样化的。从行政附属上看，生物样品库涵盖了政府机构、医院、高校和研究所、私立公司创办的样品机构。从盈利角度看，生物样品库有非盈利型和盈利型的；从样品覆盖上看，有覆盖多个领域的综合型和只覆盖某个领域的专项型样品库。根据最新的国际生物样品库目录[9]，生物样品库在北美和欧洲各有 100 家以上，在亚洲有 22 家，其中中国有三家。这些都是正规的、门类齐全的综合型生物样品库。

除了生物样品库本身，还有为此服务的生物样品库中介公司（Biobank Brokers）。这些机构大多是商业公司，利用生物样品库的信息共享渠道，建立了自己的样品目录，利用自己的渠道来推广生物样品库中的样品，中介有的也有自己的产品，但是大多数没有自己的产品。可以肯定的是，中介的目录要远大于自己有的样品。这些中介最近几年内在欧美迅速发展，这个现象从商业角度说明了生物样品库有市场需求和盈利空间。

面临挑战，前景宽广

生物样品库作为一个新的产业，目前面临着三大挑战：

第一：伦理和法律方面；

第二：管理和规范；

第三：运营、资金支持和可持续性。

在伦理和法律方面，生物样品库引发了非常多的讨论，归根结底这些讨论聚焦在患者个体的私密信息保护、分享权以及这些信息和权力的转让和商业化处理上[10-17]。随着分子生物学的进展、大规模测序技术和大数据技术的进步，这些问题可能引发激烈的辩论和不确定性。在这个方面，生物样品库的信息部分比它的实体部分更加引人关注。

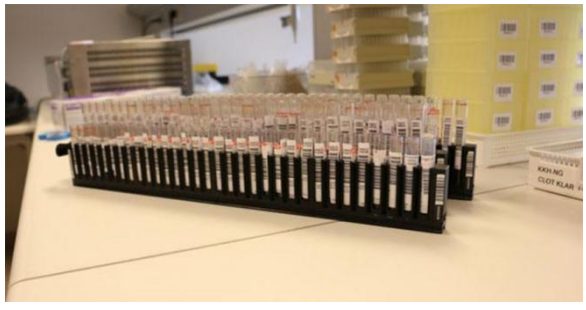
在管理和规范方面，因为生物样品库的门类繁多，在各个不同的机构、地区、国家和国际机构里，都有不同的操作和标准，因此在管理方面的首要任务是协调各类标准以达成共识[18-24]。

在运营方面，各类生物样品库是否有足够的资金支撑和是否可持续运营，也是一大挑战。目前大部分的生物样品库所面

向的市场是科研，所以生物样品库基本上也是靠着科研基金来支撑，还没有做到自我造血和独立存活，也没有进入商业运营模式。

生物样品库和液体活检相辅相成

生物样品库的存在和发展，显著地推动了生物标记物的开发和确认，继而推动了以生物标记物为基础的癌症检测和治疗的领域[25-33]。癌症的诊疗目前已经进入分子水平，人们充分接受了这样的医学事实，就是癌症是上百种不同的病种的总和，而每一种癌症都有独特的检测方案，这些检测方案和特定的癌症所呈现出的生物标记物的组合是直接相关的。虽然 FDA 迄今为止只批准了少数的生物标记物作为明确接受的癌症诊断依据（比如 EGFR 突变来诊断非小细胞肺癌），但是在科研领域有大量的生物标记物及其组合，已经成为诊断各类癌症的首选方法。



这些生物标记物不是静态存在，而是动态变化的，不停地有新的生物标记物被发现、评估和确认，这些发现、评估和确认的过程，是离不开生物样品库的推动的。生物标记物的发现，可以是在基础研究的实验室内，一旦发现的过程完成了，即进入临床确认阶段，如果没有生物样品库来提供大量的特定类型的癌症样品，这个临床确认过程将通过招募患者启动临床研究来完成，那将是非常昂贵和漫长的。所以说，生物样品库显著地推动了生物标记物的开发和确认。

生物样品库的存在和发展，也显著地推动了个体化医疗的发展[34-44]。癌症的高突变性决定了癌症的诊断和治疗必将是在个体基础上的，个体化医疗的最合适的领域正是癌症领域。对于每一个患者，肿瘤的发生、复发和消退的动态变化，都应该记录在案。每一次的取样和储存，如果是血液样品，即是液体活检操作。这些液体活检的样品在完成检测后，不是要丢弃而是要进入生物样品库，成为这名患者的个体化诊疗的留样。这样，生物样品库成为了液体活检的延伸，也为专注于样品采集和储存的样品专家们，提出了新的挑战，因为这时的样品储存有了更高的要求，不再是稳定几天和几星期，而是稳定几年或更久。

通过生物标记物和个体化诊疗这两个概念，生物样品库和液体活检互相重叠，互补促进，相辅相成。

参考文献

1. Park A et al. 10 ideas changing the world right now. Time. 2009; 173(11).
2. Davey Smith G et al. Genetic epidemiology and public health: hope, hype, and future prospects. Lancet. 2005 Oct 22-28; 366(9495): 1484-98.
3. Vaught J et al. The evolution of biobanking best practices. Clin Chim Acta. 2012 Oct 9; 413(19-20): 1569-75.
4. Hallmans G et al. Best practices for establishing a biobank. Methods Mol Biol. 2011; 675: 241-60.
5. Vaught J et al. Biobanking Comes of Age: The Transition to Biospecimen Science. Annu Rev Pharmacol Toxicol. 2016; 56: 211-28.
6. Somiari SB et al. The Future of Biobanking: A Conceptual Look at How Biobanks Can Respond to the Growing Human Biospecimen Needs of Researchers. Adv Exp Med Biol. 2015; 864: 11-27.
7. Zisis K et al. Biobanking with Big Data: A Need for Developing "Big Data Metrics". Biopreserv Biobank. 2016 Oct; 14(5): 450-451.
8. Sudlow C et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015 Mar 31; 12(3): e1001779.
9. Online publication et al. Global Biobank Directory, Tissue Banks and Biorepositories http://specimencentral.com/biobank-directory/.
10. Vaz M et al. Ethical challenges in biobanking: moving the agenda forward in India. Indian J Med Ethics. 2014 Apr 1; 11(2): 79-88.
11. Zika E et al. Sample, data use and protection in biobanking in Europe: legal issues. Pharmacogenomics. 2008 Jun; 9(6): 773-81.
12. Bledsoe MJ et al. Ethical Legal and Social Issues of Biobanking: Past, Present, and Future. Biopreserv Biobank. 2017 Apr; 15(2): 142-147.
13. Caulfield T et al. Genes, cells, and biobanks: Yes, there's still a consent problem. PLoS Biol. 2017 Jul 25; 15(7): e2002654.
14. Tassé AM1 et al. Biobanking and deceased persons. Hum Genet. 2011 Sep; 130(3): 415-23.

15. De Clercq E1 et al. Returning Results in Biobank Research: Global Trends and Solutions. Genet Test Mol Biomarkers. 2017 Mar; 21(3): 128-131.

16. Moodley K et al. "It's all about trust": reflections of researchers on the complexity and controversy surrounding biobanking in South Africa. BMC Med Ethics. 2016 Oct 10; 17(1): 57.

17. Hartlev M et al. Genomic Databases and Biobanks in Denmark. J Law Med Ethics. 2015 .

18. NCI Best Practices for Biospecimen Resources. https://biospecimens.cancer.gov/bestpractices/2016-NCIBestPractices.pdf.

19. Biorepositories and Biospecimen Research Branch at national Cancer institute. https://biospecimens.cancer.gov/default.asp.

20. OECD et al. Guildlines on human biobanks and genetic research databases. https://www.oecd.org/sti/biotech/44054609.pdf.

21. Staunton C et al. Challenges in biobank governance in Sub-Saharan Africa. BMC Med Ethics. 2013 Sep 11; 14:35.

22. Wei BR et al. Digital pathology and image analysis augment biospecimen annotation and biobank quality assurance harmonization. ClinBiochem. 2014 Mar; 47(4-5): 274-9.

23. Peakman T et al. Current standards for the storage of human samples in biobanks. Genome Med. 2010 Oct 5; 2(10): 72.

24. Adishesh M et al. Harmonisation of biobanking standards in endometrial cancer research. Br J Cancer. 2017 Aug 8; 117(4): 485-493.

25. Kang HJ et al. Identification of clinical biomarkers for pre-analytical quality control of blood samples. Biopreserv Biobank. 2013 Apr; 11(2): 94-100.

26. Kalia M et al. Biomarkers for personalized oncology: recent advances and future challenges. Metabolism. 2015 Mar; 64(3 Suppl 1): S16-21.

27. Kenner BJ et al. Early Detection of Pancreatic Cancer: The Role of Industry in the Development of Biomarkers. Pancreas. 2017 Sep 26. doi: 10.1097 (Epub).

28. Berger KN et al. PD-1 pathway and its clinical application: A 20year journey after discovery of the complete human PD-1 gene. Gene. 2017 Sep 23. pii: S0378-1119(17)30782-5.

29. D'Oronzo S et al. The role of biomarkers in the management of bone-homing malignancies. J Bone Oncol. 2017 Sep 11; 9:1-9.

30. Jung K et al. Comparison of 10 serum bone turnover markers in prostate carcinoma patients with bone metastatic spread: diagnostic and prognostic implications. Int J Cancer. 2004 Sep 20; 111(5): 783-91.

31. Bhargava A et al. Epigenetic biomarkers for risk assessment of particulate matter associated lung cancer. Curr Drug Targets. 2017 Sep 10 (Epub).

32. Chang L et al. Microsatellite Instability: A Predictive Biomarker for Cancer Immunotherapy. Appl Immunohistochem Mol Morphol. 2017 Sep 4 (Epub).

33. Schrohl AS et al. Banking of biological fluids for studies of disease-associated protein biomarkers. Mol Cell Proteomics. 2008 Oct; 7(10): 2061-6.

34. Kinkorová J et al. Biobanks in the era of personalized medicine: objectives, challenges, and innovation: Overview. EPMA J. 2016 Feb 22; 7-4.

35. Liu A et al. Biobanking for Personalized Medicine. AdvExp Med Biol. 2015; 864: 55-68.

36. Liu A et al. Developing an institutional cancer biorepository for personalized medicine. ClinBiochem. 2014 Mar; 47(4-5): 293-9.

37. Betsou F et al. Human biospecimen research: experimental protocol and quality control tools. Cancer Epidemiol Biomarkers Prev. 2009 Apr; 18(4): 1017-25.

38. Sun S et al. Patient-derived xenograft platform of OSCC: a renewable human bio-bank for preclinical cancer research and a new co-clinical model for treatment optimization. Front Med. 2016 Mar; 10(1): 104-10.

39. Riondino S et al. Ensuring Sample Quality for Biomarker Discovery Studies - Use of ICT Tools to Trace Biosample Life-cycle. Cancer Genomics Proteomics. 2015 Nov-Dec; 12(6): 291-9.

40. Almasi M et al. Biobanking - the First Step to Successful Liquid Biopsy Experiments. KlinOnkol. 2017 Summer; 30(Supplementum2): 9-12.

41. Lee S et al. Prognostic Significance of Host-related Biomarkers for Survival in Patients with Advanced Non-Small Cell Lung Cancer. J Cancer. 2017 Aug 25; 8(15): 2974-2983.

42. Basik M et al. Biopsies: next-generation biospecimens for tailoring therapy. Nat Rev ClinOncol. 2013 Aug; 10(8): 437-50.

43. Cervo S et al. Cost-effective organization of an institutional human cancer biobank in a clinical setting: CRO-Biobank experience toward harmonization. Int J Biol Markers. 2015 May 26; 30(2): e243-51.

44. Bins S et al. Implementation of a Multicenter Biobanking Collaboration for Next-Generation Sequencing-Based Biomarker Discovery Based on Fresh Frozen Pretreatment Tumor Tissue Biopsies. Oncologist. 2017 Jan; 22(1): 33-40.

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Article Abstract Collection

文献摘要

本期的文献摘要，选取了专家综述中的若干重要的引用文献，针对综述做了中文翻译。这些文章代表了生物样品库的概念、现状、前景，以及最新进展。

参考文献摘要翻译

1. **Davey Smith G et al. Genetic epidemiology and public health: hope, hype, and future prospects. Lancet. 2005 Oct 22-28; 366(9495): 1484-98.**

摘要

流行病学是一个快速发展的研究领域，但是对于个体或群体的相关研究结论还尚未明确。分子遗传筛查的应用在某些单基因疾病中是合理的，但是关于常见的复杂疾病还没有确定的价值。基于分子遗传检测的针对常见疾病的个体化医疗还没有发展起来。通过孟德尔随机化方法的应用，遗传流行病学有助于评估环境可变的风险因素的内在原因，因此有助于寻找适当的预防策略。技术上的和其他方面的进步将使得遗传流行病学的潜力在接下来的几年中发挥出来，并且为这些研究建立以大的群体为基础的资源（生物样品库），以更好的为这些研究做贡献。

2. **Vaught J et al. The evolution of biobanking best practices. Clin Chim Acta. 2012 Oct 9; 413(19-20): 1569-75.**

摘要

对于许多临床和基础研究领域来说，生物样品库和生物样品是重要的组成部分。生物样品的数量和相关的数据必须是一致的并且要根据标准的方法来收集，以避免错误的分析结果。这些错误的分析结果可能导致无效的研究结论变成有效的研究结论。许多国际协会已经倡导发展和发表最优方法，这些最优方法包括在处理样品方面的技术上的建议和生物样品库中道德和规章上的实践。这些指导资料有助于保持在生物样品整体的一致性和提升研究质量。然而，最优方法在国际协调的缺失、难以一帆风顺的采用和监管不足正在阻止着生物样品质量、合作者和生物样品库网络协调性的进一步发展。相比于更加直接的技术和管理问题，道德和法规的实践通常包括更加有争议的和难以标准化的问题。

3. **Hallmans G et al. Best practices for establishing a biobank. Methods Mol Biol. 2011; 675: 241-60.**

摘要

生物样品库可以定义为用于研究或临床目的的生物样品的长期储存。除了存储设施，生物样品库可能由生物样品、数据、员工、政策、处理样品程序和提供其它服务

这样一个完整的组织组成，例如，数据库的管理和科学研究计划。设施、政策和处理方法的结合也可以称为生物资源中心（BRC）（www.iarc.fr）。使用生物样品库中的样品进行的研究受欧盟（EU）建议（在人生物材料研究上的建议。在人生物材料研究上的建议草案在CDBI的2005年10月20日的全体会议上通过）的管控，并且由美国国家癌症协会的自愿最佳行动管控（NCI）（http://biospecimens.cancer.gov）和其它组织管控。研究型生物样品库的管理根据协会和国际规章不同而不同。然而，有许多协议的地区已经有了应该遵循的最佳实践，以建立有高质量的样品和数据的生物样品库。

4. **Vaught J et al. Biobanking Comes of Age: The Transition to Biospecimen Science. Annu Rev Pharmacol Toxicol. 2016; 56: 211-28.**

摘要

生物样品库包括采集、处理、存储和生物样品的分布，并且有必要建立政策和程序以成功实现这些目的。尽管生物样品库可能也包括环境研究或者档案的收集，大部分生物样品库实践的统一已经向着人类生物医学研究的方向发展。最初主要集中在病理学中用于诊断的样品的收集，现在生物样品库在致力于推进个体化（或精准）药物和转化研究的许多其它组织有应用。这种发展已经包括生物样品库最佳实践的发展和生物样品科学新兴的领域的以实验为依据的方法驱动的一个领域的转变。基于证据的实践来收集可以自信地与国际合作者分享的生物样品和数据已经变得越来越重要。除了这些技术方法以外，其它的因素也有着重要的作用，例如道德和规章问题、商业计划和可持续性、数据收集和分享的方法等。

5. **Somiari SB et al. The Future of Biobanking: A Conceptual Look at How Biobanks Can Respond to the Growing Human Biospecimen Needs of Researchers. Adv Exp Med Biol. 2015; 864: 11-27.**

摘要

人生物样品的生物样品库，已经从简单的私人收集的、往往注释很少的残留的临床的样品，发展成为由商业私人机构和非赢利性机构进行详细注释的、有组织的收集。生物样品库的活动目前集中于国际的和政府代理，这是为了认可为产业的提供采取最佳实践和提供科学的、道德的、合法的指导原则的需求。还有更多的需求，比如高质量的、临床注释的生物样品的数量会增多，这首先是由于空前水平的基因组的、后基因组的和个体化药物研究活动的进行。对于更多生物样品的需求提供了新的挑战和机遇，寻找策略来构建生物样品库并发展成一门生意，以便在未来能更好的满足生物样品的需求。在组织和资金方面需要思考模式的变化，还有如何、去哪收集、储存生物样品和分配。名叫Research Ready Hospitals （RRHs）的新的收集点和新的公私合营模式可以提高生物样品的持续性和有效性。生物样品库将会采取全行业范围的标准操作程序，更好的和非破坏性的方法用于质量评估，成本更低的方法用于样品储存/分配和客观的方法来管理稀有的生物样品。最后，未来生物样品库的成功将依赖于公私合营模式的成功、可获得生物样品的数量和多样性、成本管理和有效的生物样品库的实现。一个有效的生物样品库是可以提供高质量和可负担的生物样品来驱动研究并且为我们提供更健康和更加高质量的生活。

6. **Zisis K et al. Biobanking with Big Data: A Need for Developing "Big Data Metrics". Biopreserv Biobank. 2016 Oct; 14(5): 450-451.**

摘要

“大数据”这个术语是一个无所不包的术语，经常被用作涉及使用大规模数据集的研究。然而，该术语的使用几乎没有表明定义、数据集的潜在复杂性以及需要考虑的可持续研究和下游影响的估计。特别是，“大数据”经常与生物样品库和生物样品库网络有关，因为涉及组织保存的机构越来越不可避免地与信息保存相关联。“大数据”通常被定义为庞大而复杂的数据集合，其操作和管理会带来重大的后勤挑战（牛津英语词典，2013年）。在临床研究领域内，这个术语通常与大型医院，临床试验和/或基于组织的财团及其相关联的银行样品的电子患者记录同义。这些数据可以是结构化的或非结构化的，由不同来源（有时是实时的）产生，并且数量非常大。

7. **Sudlow C et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015 Mar 31; 12(3): e1001779.**

摘要

总结点

- 英国生物样品库是一项非常庞大而详细的前瞻性研究，在 2006-2010 年招募时，有超过 500,000 名 40-69 岁的参与者。
- 该研究收集并继续收集与参与者有关的大量的表型和基因型详情，包括问卷调查、物理测量、样品分析、加速度测量、多模式成像、全基因组基因分型和纵向随访，以得到广泛的健康相关的结果。
- 广泛的咨询，来自科学、管理、法律和伦理合作伙伴的意见，和工业规模的集中流程对于开发这种资源至关重要。
- 英国生物样品库可实现开放性获取，无需合作，任何希望开展与公众利益相关的健康相关研究的真正的研究人员都可以使用它。

8. **Vaz M et al. Ethical challenges in biobanking: moving the agenda forward in India. Indian J Med Ethics. 2014 Apr 1; 11(2): 79-88.**

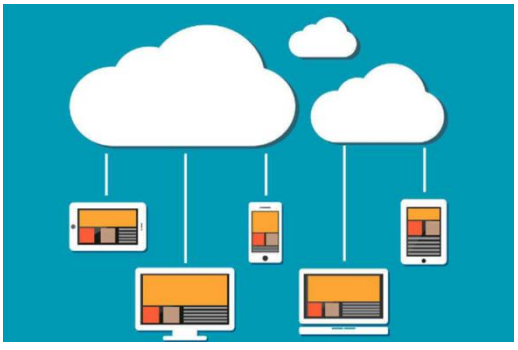
摘要

关于生物样品的类型和定义尚未达成共识。包括印度在内的各国现行法规都侧重于基因组和基因数据库以及 DNA 和细胞系的生物样品。目前尚不清楚生物样品在诊断和研究实验室中的保存将如何被这些监管框架监管。由于样品储存和数据处理的进展，对人类基因组的更深入理解以及高通量实验室检测和生物样品库相关研究变得非常有吸引力。对于问题上已经有大量的文献和大量的讨论，特别是在发达国家的伦理和监管的难题上。但这并非仅是发展中国家的情况。本文基于对已发布的文件和数据的审查，旨在评估印度背景下生物样品库的道德框架。讨论了“广泛同意”、“样品商业化”和“扩大样品使用”等问题，生物样品库的管理作为制度和伦理责任的一个组成部分出现，也使得国家准则的实施成为可能，并有助于加强信任和当地的贡献者在生物样品库的研究中的信心。

9. **Zika E et al. Sample, data use and protection in biobanking in Europe: legal issues. Pharmacogenomics. 2008 Jun; 9(6): 773-81.**

摘要

共享存储使得用于研究的生物样品库中的样品和数据对捐助者的隐私产生了影响，但也引发了有关欧洲内部研究监管的问题。欧洲的许多法律文件和准则对生物样品库产生直接影响，但是还没有专门为支持这一活动而制定的法律文件和准则。此外，虽然在国家级别设立了一些新的规定，但这些法律文书的定义、范围和目的还有很多差异。这对基因组研究造成了不必要的障碍，特别是在样品跨国界共享的情况下。目前还有一个问题，即是否需要为生物样品库设计新的、具体的立法和治理框架，或者是否足以修改现行的一般法律并制定具体的指导方针，或者在当前法规中适应生物样品库提出的问题。因此，一个集结了来自学术界和业界专家、律师、国家数据保护机构、欧盟委员会和欧洲数据保护主要代表的研讨会召开了，以审查生物样品库的现有法律瓶颈和未来需求，特别是收集、交换和样品、数据的联系。本报告介绍了 2007 年 3 月在西班牙塞维利亚举行的研讨会的演讲和讨论的重点以及随后的结论。研讨会侧重于存储在生物样品库中的数据和样品的内部联系，以及生物样品库与二级信息资源（如癌症登记处）的外部联系。



10. **Bledsoe MJ et al. Ethical Legal and Social Issues of Biobanking: Past, Present, and Future. Biopreserv Biobank. 2017 Apr; 15(2): 142-147.**

摘要

在过去的 15 年中，研究环境发生了相当大的变化。这些变化包括开发新的复杂的遗传和基因组技术，包含大量基因型和表型数据的数据库的扩散，以及在国内和国

际许多机构之间共享的广泛的数据。这些变化引发了关于如何最好地保护生物样品库研究参与者的新问题。针对这些问题，已经制定了解决生物样品库法律，伦理和社会问题的最佳做法。此外，还制定了与生物样品库有关的新的道德准则，以及关于隐私和个人保护的新规定。最后，科学和研究环境的变化已经引发了与生物样品库有关的复杂的道德问题，例如关于用于生物样品库的研究、商业用途和所有权问题的最合适的同意模式的问题，以及是否以及如何将个别研究结果返还给生物样品库参与者。本文回顾了过去 15 年来与生物样品库 ELSI 相关的一些发展情况，展望未来。

11. Caulfield T et al. Genes, cells, and biobanks: Yes, there's still a consent problem. PLoS Biol. 2017 Jul 25; 15(7): e2002654.

摘要

从研究角度来看，研究者对生物样品库的兴趣不断增加。政府和工业界已经在生物样品库投入了大量资金，例如英国生物样品库和美国精准医药倡议等举措。但尽管有这种热情，许多更深层次的法律和道德挑战仍未解决。实际上，关于如何最好地获得同意以及研究参与者保留的捐赠样品和健康信息的控制程度和性质，仍然存在分歧。新兴的社会趋势，包括对商业化和继续控制权的认知（“biorights”），可能会加剧这些问题。

12. Tassé AM1 et al. Biobanking and deceased persons. Hum Genet. 2011 Sep; 130(3): 415-23.

摘要

早期的生物医学的研究主要集中在小组中活体研究参与者中的特定疾病或疾病集合。因此，管理生物医学研究的第一个伦理框架涉及活体研究参与者的短期、有限范围的研究。由于研究者近期对纵向人口的研究和生物样品库的兴趣，研究日益变得长期。这种转变引发了一些关于参与者死亡对研究影响的伦理和法律问题。本文在纵向生物淘汰基因研究的背景下概述了这些问题。我们的第一部分概述了规范参与者死亡对同意的影响的法律和道德框架。随后将分析指导已故参与者的数据和样品的二次使用以及将已故参与者的个人研究结果返还给生物家庭成员的法律和道德框架。在第二部分中，我们将回顾当前的文献，并在结束之前使用生物伦理学的“原理”理论讨论上述问题。

13. De Clercq E1 et al. Returning Results in Biobank Research: Global Trends and Solutions. Genet Test Mol Biomarkers. 2017 Mar; 21(3): 128-131.

摘要

在世界各地的许多国家，生物样品库已成为开展生物医学研究的关键资源，促进包括国际合作在内的多种研究。这一特殊问题的焦点在于一个迫在眉睫的道德问题——这个问题已成为争论的焦点——将研究成果和偶然发现返回给生物样品库参与者。虽然研究这个问题的文章没有在回归结果的背景下出现的道德，法律和社会困境提供最终答案，但是收集的目的是从多个角度和国际背景下处理这个问题，跨越英国、欧洲大陆，包括东欧、美国和中东。

14. Hartlev M et al. Genomic Databases and Biobanks in Denmark. J Law Med Ethics. 2015.

摘要

丹麦的生物样品库业务通过患者的权利法律、数据保护法律和研究伦理审查进行规范。根据数据保护法，丹麦法律承认组织样品为个人数据，这意味着根据收集的情况，用组织样品进行的研究可能受到研究伦理审查、数据保护法和患者权利要求的限制。然而，尽管信息性质相似，通过全基因组测序获得的信息的研究仅受数据保护法律的约束。从患者收集的生物样品库样品处理的监

管框架不同于从研究参与者那里收集的样品，特别是在自治方面。重要的是，为未来未明确的研究而建立的生物样品库不受研究伦理审查。基于生物样品库的研究最近在国家层面获得了越来越多的重视，并且可能出现较少碎片化和更一致的管理方法。

15. **Wei BR et al. Digital pathology and image analysis augment biospecimen annotation and biobank quality assurance harmonization. Clin Biochem. 2014 Mar; 47(4-5): 274-9.**

摘要

生物知识库最佳实践的标准化将提高利用患者衍生生物样品标本的翻译生物医学研究的质量。生物样品库增加的病理学质量保证程序已经落后于生物样品研究和生物样品库开发的其他途径。对于生物知识库样品的细胞层面的理解对于发现用于诊断和治疗的组织特异性临床相关生物标志物是非常重要的。尽管快速兴起的分子分析和数据挖掘技术将重点放在了最大限度地减少分析前过程中人为因素引起的变量，但是对生物样品的构成的注释以更有效地选择样品却很少受到关注。分析前组织处理和样品组成都会影响用于下游测定的相关大分子的获取。作为质量保证程序一部分，生物知识库提交的病理学家评论（特别是组织），有助于确保预期的靶细胞以足够数量存在于所增加的标本中。这个手动程序可能是单调和主观的。将数字病理学纳入生物样品库质量保证程序中，使用自动模式识别形态测量图像分析来量化组织切片图像的整个幻灯片图像中的组织特征区域，可以最大限度地减少与生物知识库中常规病理评估相关的变异性和主观性。向研究人员提供全片幻灯片图像和病理学家评估的形态分析，可以指导样品选择。使病理学质量保证方法协调一致，最大限度地降低主观性并提高收集样品之间的可重复性，将有助于调查人员选择与研究有关的标本，并可促进以综合网络方法进行生物样品库的信息共享。

16. **Peakman T et al. Current standards for the storage of human samples in biobanks. Genome Med. 2010 Oct 5; 2(10): 72.**

摘要

生物样品库的设计和目的各不相同，完全协调过去和未来的生物样品库的想法是无法承受和不可行的。生物样品库应该集中精力开发和维护能够提供广泛生物信息的高质量样品集，这些样品将引入最小化的变异性。还应提供样品处理、存档和质量控制程序的全面数据审核跟踪。这将使生物样品库的数据能够作为与其他类似资源进行更广泛合作的一部分。

17. **Kang HJ et al. Identification of clinical biomarkers for pre-analytical quality control of blood samples. Biopreserv Biobank. 2013 Apr; 11(2): 94-100.**

摘要

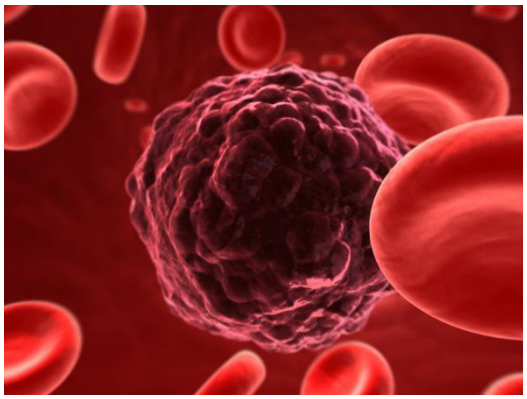
背景：分析前条件是维持生物样品高质量的关键因素。它们对于在生物标志物发现领域的实验的精确再现性以及实现用于临床诊断的实验室测试的最佳特异性是必需的。在韩国国家生物样品库的研究中，我们通过测量临床实验室检测中常用的生化分析物，评估了分析前条件对生物标记血液样品稳定性的影响。

方法：我们用全自动化学分析仪（Hitachi 7600-110）测量了来自健康供体（n=50）的血清和血浆样品中的 10 种常规实验室分析物。根据血液分馏的延迟、分馏血清和血浆样品的冷冻延迟以及在不同的冻融循环（0、1、3、6、9）下进行的分析物测量。使用重复测量 ANOVA 和显著变化极限（SCL）来确定与参考样品平均值相比的统计学显著变化。

结果：根据血液收集和分离之间的时间间隔以及血清和血浆样品的分馏和冷冻之间的时间间隔，GGT 和 LDH 的在血清水平上发生了显著改变。血糖水平仅对血液分

离的血液收集和离心之间经过的时间最敏感。基于这些发现，可以推导出一个简单的公式（葡萄糖每小时减少1.387mg/dL）以估计采血后延迟的时间长度。另外，AST、BUN、GGT 和 LDH 显示出对血清和血浆样品的反复冻融循环的敏感反应。

结论：这些结果表明，GGT 和 LDH 的测量可用作用于某些分析前条件（例如，延迟处理或反复冻融）的质量控制标记，可以直接用于生物样品库未来实验室测试或存储的研究。



18. **Kalia M et al. Biomarkers for personalized oncology: recent advances and future challenges. Metabolism. 2015 Mar; 64(3 Suppl 1): S16-21.**

摘要

癌症是一种疾病，其特征在于异常细胞的不受控制的生长和扩散，肿瘤学是处理肿瘤的医学分支。近十年来，肿瘤生物标志物的发展取得了重大进展，这在理解驱动肿瘤的发生、维持和进展的分子和细胞机制方面发挥着关键作用。随着我们开始了解将正常细胞转变为异常细胞的复杂机制，肿瘤学领域的临床分子诊断和生物标志物的发现正在迅速发展。这些发现推动了新型药物靶点和新的治疗策略的发展。晚期癌症患者的治疗标准已经从基于临床病理学特征的经验性治疗策略转移到使用基于肿瘤分子特征的生物标志物驱动治疗算法的治疗策略。多重基因分型技术和新一代高通量测序技术的最新进展使得可以快速全面地分析个体患者的癌症基因组，甚至可以从很少的肿瘤活检材料中进行分析。预测性（诊断性）的生物标志物有助于将靶向治疗与患者相匹配以及预防标准（系统）治疗的产生的毒性。预后生物标志物可以鉴定血液中体细胞的突变、DNA 甲基化的改变、microRNA（miRNA）和循环肿瘤细胞（CTC）的升高水平。使用分子诊断学的预测性生物标志物目前正在用于治疗五种疾病的个体化癌症疗法的临床实践中：慢性粒细胞白血病、结肠癌、乳腺癌、肺癌和黑素瘤，并且这些生物标志物正被成功用于评估可通过靶向治疗实现的益处。这些分子靶向生物标志物疗法的例子有：慢性粒细胞白血病和胃肠道肿瘤中的酪氨酸激酶抑制剂；具有 EML4-ALk 融合的肺癌中的间变性淋巴瘤激酶（ALK）抑制剂；HER2/neu 阳性乳腺癌中的 HER2/neu 阻断和表皮生长因子受体（EGFR）抑制 EGFR 突变肺癌。这篇综述介绍了在我们选择的 5 种癌症中的生物标志物的现状：慢性粒细胞白血病、结直肠癌、乳腺癌、非小细胞肺癌和黑色素瘤。

19. **Kenner BJ et al. Early Detection of Pancreatic Cancer: The Role of Industry in the Development of Biomarkers. Pancreas. 2017 Sep 26. doi: 10.1097 (Epub).**

摘要

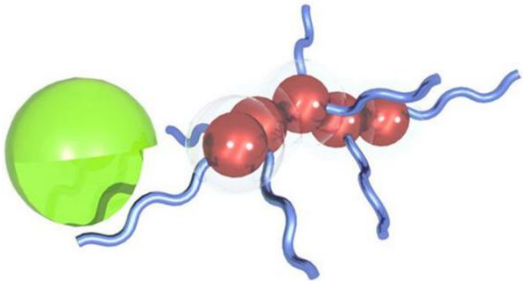
胰腺癌的预后较差，其 5 年生存率仅为 9%。目前，大多数人被诊断为晚期，晚期治疗的选择是有限的。胰腺癌的早期发现提供了极大的希望，使生存率大幅改善。与美国胰腺协会合作的肯纳家族研究基金会发起了一系列论坛，以促进胰腺癌早期检测的讨论和合作。在 2014 年的第一个论坛“散发性胰腺癌早期检测峰会”上，一个跨学科的国际科学代表小组提出了一个战略计划，随后产生了创新的战略地图。目前的会议报告是“胰腺癌的早期发现：产业在生物标记物开发中的作用”系列的第三个论坛，该论坛于 2016 年 10 月 27 日在马萨诸塞州波士顿举行。该报告提供了行业创新举措的实例，并证实了工业、政府、研究机构和倡导团体之间协作的迫切需要，以使胰腺癌在早期阶段更容易被检测到。

20. **Berger KN et al. PD-1 pathway and its clinical application: A 20year journey after discovery of the complete human PD-1 gene. Gene. 2017 Sep 23. pii: S0378-1119(17)30782-5.**

摘要

抗 PD-1 治疗是一种新的免疫检查点抑制疗法，在治疗难治性/复发性癌症方面具有巨大潜力。人类 PD-1 研究的 20 年历程经历了 3 个阶段：（1）发现 PD-1 基因的结构和基因组结构；（2）了解 PD-1 介导的免疫检测点调控机制与配体（PD-L1 和 L2）；（3）通过 PD-1 免疫检查点途径将 PD-1 基因的知识转化为稳健的临床抗

癌方法。人类 PD-1 基因研究的成功反映了现代生物医学研究从实验室到临床的进步和发展趋势。然而，我们了解 PD-1 基因的旅程还没有完成。临床调查数据显示，不同类型的癌症对 PD-1 免疫抑制点抑制治疗的反应率高，范围为 18%至 87%。没有可靠的生物标志物来预测个别患者对 PD-1 抑制性免疫治疗的反应。患者可具有 PD-1 免疫检查点抑制治疗的原代、适应性或甚至获得性抗性。此外，新的数据表明，某些患者在接受 PD-1 免疫检查点抑制治疗后经历超进展性疾病状态。综上所述，PD-1 免疫检查点抑制治疗开辟了晚期肿瘤免疫治疗的新领域。同时，在基本的科学机制研究和临床研究中，还需要进一步运用个性化和精准医学的原则。



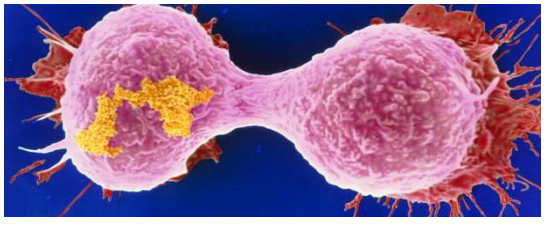
21. D'Oronzo S et al. The role of biomarkers in the management of bone-homing malignancies. J Bone Oncol. 2017 Sep 11; 9: 1-9.

摘要

骨髓是集中实体肿瘤的常见转移部位，包括乳腺癌，前列腺癌和肺癌恶性肿瘤转移。骨转移（BM）的发生不仅与严重的骨骼并发症有关，而且还缩短了总生存期，因为晚期癌症缺乏有效的治疗选择。

尽管诊断技术不断发展进步，BM 检测经常出现在有症状的阶段，旨在早期识别高危患者。为了这个目的，骨转换和肿瘤衍生标志物被研究其潜在的诊断、预后和预测作用。

在这篇综述中，我们总结了 BM 在乳腺癌、前列腺癌和肺肿瘤中的发病机制，同时探讨了 BM 生物标志物的鉴定和临床验证的研究现状。



22. Jung K et al. Comparison of 10 serum bone turnover markers in prostate carcinoma patients with bone metastatic spread: diagnostic and prognostic implications. Int J Cancer. 2004 Sep 20; 111(5): 783-91.

摘要

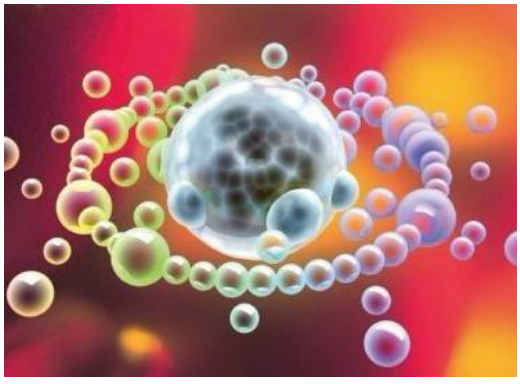
我们的目的是评估骨标志物在前列腺癌（PCa）患者早期诊断骨转移的诊断准确率及其作为预测 PCa 导致死亡率的有用性。117 例 PCa 患者血清（pN0M0，n = 39；pN1M0，n = 34；M1，n = 44），35 例健康男性和 35 例良性前列腺增生，骨形成标志物 [骨特异性碱性磷酸酶（tALP，bALP）、I 型胶原氨基端前肽（p1NP）、骨钙素（OC）]、骨吸收标志物 [骨唾液酸蛋白（BSP）、交联 C-末端（CTX）和交联型 N-末端（NTX）I 型胶原端肽、抗酒石酸酸性磷酸酶同工酶 5b（TRAP）] 和破骨细胞发生标志物 [骨保护素（OPG）、核 FAC 受体激活剂）和测定核因子-kB 受体激动剂（RANKL）]。与未转移的 PCa 患者相比，骨转移癌患者 tALP、bALP、BSP、P1NP、TRAP、NTX 和 OPG 均显著升高。OPG 显示了区分这些患者的最佳鉴别能力。Logistic 回归分析结果显示 OPG 和 TRAP 作为预测骨转移的变量，总体正确分类为 93%。OPG、P1NP、tALP、bALP、BSP、NTX、TRAP 和 CTX 浓度高于截断水平的患者比低标记浓度的患者生存期明显缩短。多因素 Cox 比例风险回归显示，仅 OPG 和 BSP 是 PCa 相关死亡的独立预后因素。因此，血清 OPG 检测骨转移扩散的重要性，单独或与其他骨标志物结合，并预测 PCa 患者的存活已经清楚地证明。

23. Bhargava A et al. Epigenetic biomarkers for risk assessment of particulate matter associated lung cancer. Curr Drug Targets. 2017 Sep 10 (Epub).

摘要

颗粒物质通过燃烧过程和风吹尘埃等直接排放到空气中，或在大气中通过发射气体的转化形成空气污染的主要因素，引发了包括肺癌在内的多种人类病。肺癌的死亡率通常较高，因为该疾病在其早期治疗阶段没有症状。此外，可用的筛选方法是昂贵的，主要依赖于缺乏足够灵敏度和特异性的成像技术。尽管在生物标志物的鉴定方面取得了进展，但是基于基因突变的方法仍然面临着严峻的挑战，因为疾病是由环境和宿主之间复杂的相互作用演变而来的。因此，表观基因组标记的识别可能有助于早期诊断，

以减少与环境相关的疾病负担。基于侵袭性“液体活组织检查”的表观基因组筛选最近出现了一种方法，它有可能在初始阶段表征肿瘤异质性。表观遗传标记（甲基化的DNA、miRNA、转录后修饰的组蛋白）已知反映了重要的细胞变化，在肺癌患者中以更高的水平循环。据报道，这些循环的生物实体与肺癌患者的临床结果密切相关，因此很有可能成为早期识别疾病的可能候选者，并监测治疗反应，从而有益于患者并改善他们的生活。然而，为了有效地实施这一策略，筛查高危人群的“护理点”测试将需要详尽的临床验证。



24. **Chang L et al. Microsatellite Instability: A Predictive Biomarker for Cancer Immunotherapy. Appl Immunohistochem Mol Morphol. 2017 Sep 4 (Epub).**

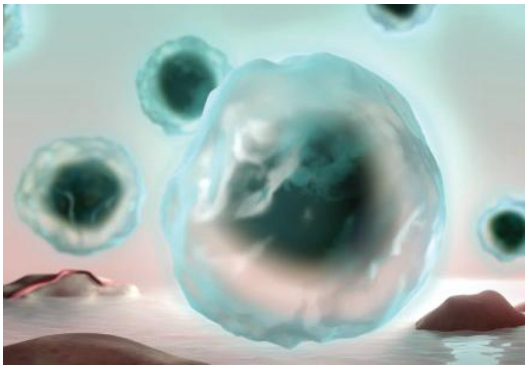
摘要

免疫治疗在各种类型的癌症中显示出有希望的结果。用于癌症免疫治疗的检查点抑制剂药物已被美国食品和药物管理局（FDA）批准用于晚期黑色素瘤、非小细胞肺癌、肾细胞癌、膀胱癌和难治性霍奇金淋巴瘤的患者。在最新的公告中，FDA 已批准对儿童和成人微卫星不稳定性高（MSI-H）或错配修复缺陷的实体肿瘤，并给予默沙东 PD-1 药物 Pembrolizumab 的加速批准。这是该机构首次批准基于共同的生物标志物而不是基于器官的方法进行的癌症治疗。由于遗传基因突变的错配修复基因或表观遗传激活这些基因，在结直肠癌和非结直肠癌中发现 MSI-H。众所周知，MSI-H 导致肿瘤细胞体细胞突变的形成，导致分子和生物学变化，包括高肿瘤突变负荷、新抗原表达增加和丰富的肿瘤浸润淋巴细胞。这些变化与检查点抑制剂药物的敏感性增加有关。在这篇迷你综述中，我们提供 MSI 相关实体肿瘤的更新，特别关注 MSI 对检查点免疫治疗的预测作用。

25. **chrohl AS et al. Banking of biological fluids for studies of disease-associated protein biomarkers. Mol Cell Proteomics. 2008 Oct; 7(10): 2061-6.**

摘要

随着个性化医疗需求的增加，个体患者对生物材料的生物需求增加。这样的样品在分子研究中是必不可少的，旨在从从流行病学的几个水平表征疾病，并且从诊断和预后分类来预测治疗的效果。临床验证的生物标志物可提供用于诊断、筛选、评估风险/易感性、评估预后、监测（疾病复发）、预测治疗反应和替代反应标记的信息。许多类型的生物流体或组织可以被收集并存储在生物反应器中。血液样品可进一步加工成血浆和血清，组织块可冷冻或固定在福尔马林中，然后嵌入石蜡中。目前的研究重点是生物流体，特别是血清和血浆，旨在研究蛋白质生物标志物。在生物标志物的研究中，从将样品取自个体到样品安全放置在生物样品库中的过程有几个阶段，包括样品的采集、样品的运输、样品的处理和存储。本综述中描述每个重要步骤中高品质生物标志物研究的关键点。未能开发和遵守稳健的标准化协议可能具有显著的后果，因为存储在生物样品库中的材料的质量以及基于这种材料的分析结论和临床建议可能受到严重影响。



26. **Kinkorová J et al. Biobanks in the era of personalized medicine: objectives, challenges, and innovation: Overview. EPMA J. 2016 Feb 22; 7:4.**

摘要

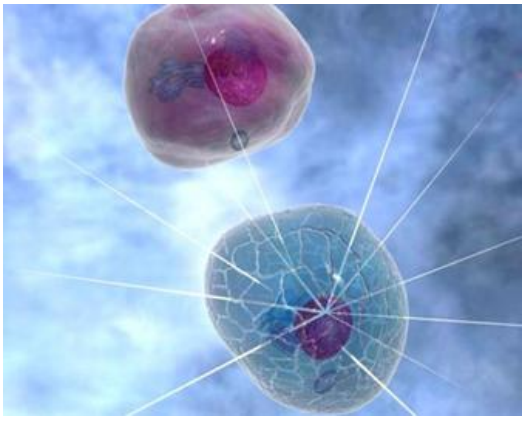
生物样品库是个体化医学的一个重要组成部分，由于个体化医学的进步，有力地支持了种群分层和生物标志物的发现和验证的科学进展。生物样品库是新药发现和药物开发的重要工具。生物样品库在患者的预防和预测、随访、治疗监测和优化的整个过程中起着重要的作用。

生物样品库的特异性在于它们涵盖了生物与医学方法相结合的多学科方法，以及生物信息学技术、计算和建模。生物样品库在过去十年中在品种和容量上从小样品集合增加到大型国家或国际储存库。收集的样品是基于人群的、疾病特异性或罕见的疾病并来源于不同的个人档案。生物样品库有多种用途，如诊断学、药理学或研究。生物样品库涉及、存储和操作特定的个人信息，因此，生物的多样性与广泛的伦理和法律问题相关。生物样品库是一种国际现象，因为目前任何一个国家或社会都无法涵盖涉及生物样品库问题的所有问题。生物样品库在二十一世纪的生物医学研究的整个过程中具有巨大的创新潜力。

27. **Liu A et al. Biobanking for Personalized Medicine. Adv Exp Med Biol. 2015; 864: 55-68.**

摘要

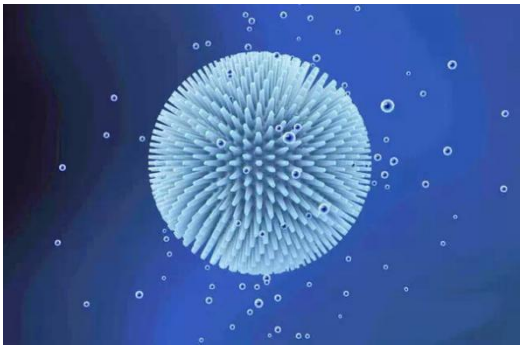
生物样品库是一个收集、处理、存储和分发生物样品及其相关数据以用于基础研究、转化研究和临床研究的实体。建立高质量人体生物样品（如组织、血液和其他体液）以及与这些样品相关的患者临床信息的生物库，为个体化医学提供了基本的科学基础建设。与特定医学病症（例如癌症、心血管疾病和神经疾病）特异性相关的生物标志物的鉴定，对于早期发现、预防和治疗疾病是非常有用的。确定个体肿瘤生物标志物，并将这些生物标志物用于疾病诊断、预后和治疗响应预测，对个体化医学具有非常显著的影响，而且正在迅速改变临床治疗的实施方式。由于个体化医学的一个关键要求是，可以提供大量附有详细患者临床和病理数据的患者样品，因此生物样品库在个体化医学的发展中起着重要作用。本章的目标是探索生物样品库在个体化医学中的作用，并讨论关于针对转化研究和临床研究——尤其是针对个体化医学发展的生物样品库开发的特定需求。



28. **Liu A et al. Developing an institutional cancer biorepository for personalized medicine. Clin Biochem. 2014 Mar; 47(4-5): 293-9.**

摘要

高质量的人体生物样品，如组织、血液、细胞衍生物和相关的患者临床信息，是支持分子生物标志物与诊断试剂发现和鉴定的科学基础建设的关键要素。大多数生物样品库的目标是收集、处理、储存和分发人体生物样品，以用于基础研究、转化研究和临床研究。作为中心枢纽的生物样品库为研究人员提供了宝贵的资源，包括通过相关患者临床信息进行适当检查和表征的生物样品。生物样品库的开发和管理通常需要标准化、质量控制和信息技术方面的专业知识，以及对前沿研究发展的认识。低成本的个体肿瘤全基因组图谱的可用性已经开创了新的可能性，使个体化医学可能以最小的毒性向个体患者提供最合适的治疗。因此，支持个体化医学的生物样品库需要最高标准的操作，以及充足的资金、培训和认证。本综述为临床研究和个体化医学发展提供了一个机构性的癌症生物样品库发展的概况。

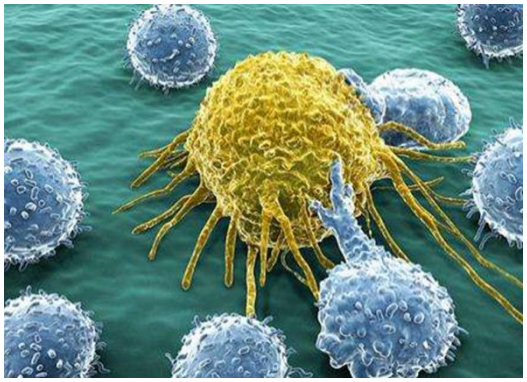


29. **Sun S et al. Patient-derived xenograft platform of OSCC: a renewable human bio-bank for preclinical cancer research and a new co-clinical model for treatment optimization. Front Med. 2016 Mar; 10(1): 104-10.**

摘要

新一代测序和生物信息学的发展，已经开始揭示包括口腔鳞状细胞癌（OSCC）在内的人类癌症基因组中复杂的遗传景观。为了了解癌症的分子多样性，并实现个体化治疗的目标，需要完全代表肿瘤内和肿瘤间异质性的复杂的临床前模型。在过去的十年中，与其他常规临床前模型相比，患者衍生的异种移植物（PDX）模型已被

证明是转化癌症研究中首选的临床前工具。PDX 模型由可以保留其供体肿瘤组织学和遗传特征的人类肿瘤样品产生。具体地说，基因明确定义的 PDX 模型可用于加速靶向抗肿瘤药物的开发和生物标志物的发现。最近，我们成功建立并表征了一个 OSCC PDX panel，作为我们用于转化癌症研究的肿瘤生物样品库的一部分。在本文中，我们将讨论 PDX 模型的建立、表征和临床前应用。我们特别关注基于确证注释的 PDX 模型的分类和应用，确证注释包括临床病理学特征、基因组图谱和药理学测试信息。近期我们还探索了这个经过充分注释的 PDX panel 在用于患者分层和治疗优化的共临床试验发展中的转化价值。虽然仍然存在各种限制，但这种临床前方法应该被进一步测试和改进。



30. Riondino S et al. Ensuring Sample Quality for Biomarker Discovery Studies - Use of ICT Tools to Trace Biosample Life-cycle. Cancer Genomics Proteomics. 2015 Nov-Dec; 12(6): 291-9.

摘要

个体化医学日益增长的需求标志着从经验医学向分子医学的转变，旨在预测对每位患者更安全有效的医疗，同时最大限度地减少不良反应。本文强调了生物标志物发现研究的重要性，并且使得样品的可用性在生物医学研究中扮演着至关重要的角色。因此，人们对生物样品库科学的极大兴趣随之而来。在生物样品库中，生物材料及其相关数据按照标准操作程序（SOPs）和现有法律进行收集、处理和存储。样品质量通过遵守 SOPs 来确保，样品的整个生命周期可以通过创新跟踪系统进行记录，这种创新跟踪系统采用了信息技术（IT）工具，用于监测储存条件和大量数据的表征。以上所有内容都将确保研究设备之间适当的样品可交换性，并且将成为未来所有个体化医学临床试验的起点。

31. Almasi M et al. Biobanking - the First Step to Successful Liquid Biopsy Experiments. Klin Onkol. 2017 Summer; 30(Supplementum2): 9-12.

摘要

生物样品库中生物材料的存档被认为是研究活动最初始、最关键的部分。大多数情况下，生物样品库是为了研究目的而建立的，因为它们允许收集足够的材料，用于分析新的生物标志物，或分析以前鉴定的生物标志物的试验。生物样品库需要快速响应研究人员和临床医生的当前需求，但这不是一个严格的系统。单克隆丙种球蛋白的实验室分析基于从患者的骨髓中分离的浆细胞。一个特别的问题是通常缺乏肿瘤细胞组分，这归因于肿瘤细胞在骨髓中的位置及其低渗透的特性。临床研究面临的挑战之一是必须改变生物样品库，以便样品允许通过所谓的液体活检来检测骨髓中以及来自周边血液的微小残留病变。本文的目的是说明归档捷克共和国生物材料的重要性，并展示其在血液肿瘤学中用法的具体应用。用于统计分析的临界数量样品的可用性，是解决许多研究问题时存在的一个普遍问题。获取临界量的生物材料样品可以通过生物样品库之间的协作快速存档，这些生物样品库共享方法学标准和研究项目样品的可用性信息。

32. Lee S et al. Prognostic Significance of Host-related Biomarkers for Survival in Patients with Advanced Non-Small Cell Lung Cancer. J Cancer. 2017 Aug 25; 8(15): 2974-2983.

摘要

这项研究确定了晚期非小细胞肺癌（NSCLC）患者中的宿主相关的生存预后生物标志物。本研究基于对 135 例病理证实的晚期 NSCLC 患者医疗记录的回顾性分析。在本研究中评估的反映患者病情的宿主相关生物标志物包括血红蛋白（Hb）水平，血小板（PLT）、嗜中性粒细胞、淋巴细胞和单核细胞计数以及铁蛋白浓度。总生存期（OS）通过 Kaplan-Meier 分析计算并使用对数秩检验进行比较。使用 Cox 比例风险回归的单因素和多因素分析来评估生存预后的效果。在登记的患者中，91.1%有 IV 期 NSCLC，42.2%的 ECOG-PS 评分为 2，57%曾经历过多轮预先的全身治疗。预后因素包括低 Hb 浓度（男性：Hb<13 g/dL，女性：Hb<12 g/dL；p=0.046）、中性粒细胞计数增加（>7700 细胞/μL；p<0.001）、淋巴细胞计数减少（≤1500 细胞/μL；p=0.011）、单核细

胞计数增加（> 800 细胞/μL；p<0.001）和高铁蛋白水平（男性：>200ng/mL，女性：>150ng/mL；p<0.001），这些因素都与低 OS 和死亡率风险增加相关。多变量比例风险模型显示，淋巴细胞计数、单核细胞计数和铁蛋白水平是独立的宿主相关生存预后标志物。单核细胞计数增加（HR，3.15；95%CI，1.64-6.04；p<0.001）和高铁蛋白水平（HR，1.81；95%CI，1.24-2.64；p=0.002）与较差的生存期显著相关，而淋巴细胞计数增加（HR，0.57；95%CI，0.40-0.83；p=0.004）则显示延长了生存期。免疫因子（如淋巴细胞和单核细胞计数以及血清铁蛋白水平）是重要的宿主相关的生存预后生物标志物，它们与晚期 NSCLC 患者的生存时间直接相关。

33. **Basik M et al. Biopsies: next-generation biospecimens for tailoring therapy. Nat Rev Clin Oncol. 2013 Aug; 10(8): 437-50.**

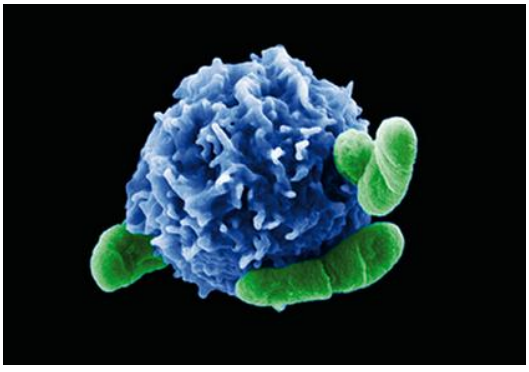
摘要

现有的肿瘤生物样品库中的大部分样品是原发性肿瘤的手术标本。对肿瘤生物学的洞察，如肿瘤内异质性、肿瘤-宿主串扰和治疗过程中疾病的演变，需要来自原发肿瘤的生物样品和那些在特定情况下反映患者疾病的生物样品。新一代“组学”技术有助于肿瘤的深层询问，但样品的特征可以确定结果的最终准确性。面临的挑战是，对肿瘤进行活检，在某些情况下是随着时间连续进行的，对于后续的分子应用，需要确保样品是有代表性的、可育活的，并且在数量和质量上都是充足的。在疾病发展轨迹期间确定的时间点收集新一代生物样品、肿瘤和血液样品，无论是用于发现研究还是指导临床决策，都会带来额外的挑战和机遇。从组织的角度来看，它还需要新增多学科治疗团队，尤其是介入放射学家、分子病理学家和生物信息学家。在本综述中，我们描述了样品采购和新一代生物样品处理的现有程序，并着重介绍了这一努力所涉及的问题，包括新一代生物样品库建设伴随的道德、后勤、科学、信息和财务方面的挑战。

34. **Cervo S et al. Cost-effective organization of an institutional human cancer biobank in a clinical setting: CRO-Biobank experience toward harmonization. Int J Biol Markers. 2015 May 26; 30(2): e243-51.**

摘要

本报告描述了意大利阿维亚诺的 CRO 阿维亚诺国家癌症研究所（CRO-Biobank）的生物样品库组织，它是一个致力于收集人体生物样品的结构化组织。它描述了一种特定的疾病特异性生物样品库和一个临床环境中研究生物样品库的整合。CRO-Biobank 的使命植根于支持和执行癌症研究，其重点在于优化技术和质量流程，同时还研究伦理、法律和 IT 论题。CRO-Biobank 实施的流程旨在保证提供者的安全、保护患者的隐私并确保其样品的可追溯性和质量。8 年的经验使我们能够提供见解和有用的建议，以解决启动新生物样品库或进一步开发现有的生物样品库时可能出现的理论和实际问题。

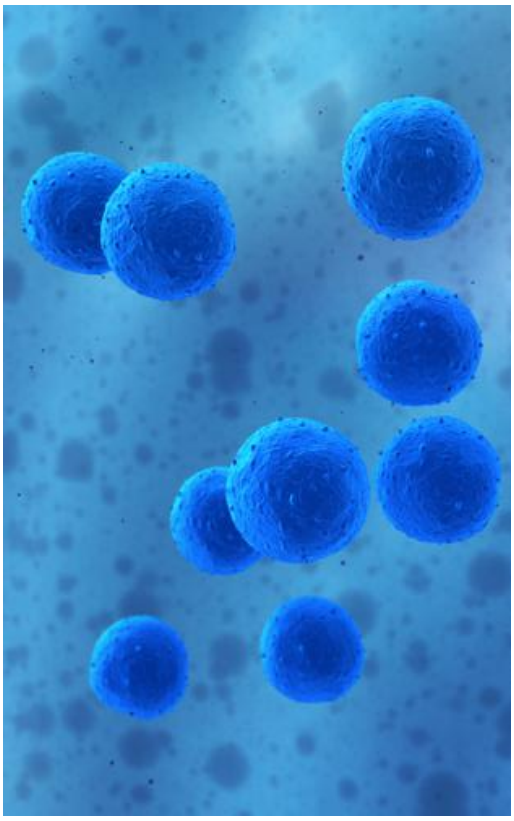


35. **Bins S et al. Implementation of a Multicenter Biobanking Collaboration for Next-Generation Sequencing-Based Biomarker Discovery Based on Fresh Frozen Pretreatment Tumor Tissue Biopsies. Oncologist. 2017 Jan; 22(1): 33-40.**

摘要

发现预测晚期癌症患者治疗响应的新型生物标志物，需要获取高质量的肿瘤样品。由于癌症随着时间的推移而发生变化，所以理想情况是在每次治疗开始之前获取组织。更优的情况是，将样品新鲜冷冻，以允许通过新一代 DNA/RNA 测序（NGS）进行分析，而且也能使其他新兴系统技术（如蛋白质组学和代谢组学）可行。在这里，我们描述了在荷兰（个体化癌症治疗中心）的一次大型合作中收集的第一批 469 个图像引导的活检生物样

品，并展示了这些生物样品用于 NGS 分析的效用。在晚期癌症患者中进行了图像引导的肿瘤活检。将样品新鲜冷冻，评估重要肿瘤的细胞性，并且在肿瘤富集区域微解剖后分离了 DNA。图像引导活检程序的安全性通过活检程序后 14 天内的一系列不良反应的报告进行评估。活检程序通常具有良好的耐受性。主要并发症的发生率为 2.1%，最常见症状的是疼痛。在 7.3%经皮肺活检中，发生了需要引流的气胸。大部分样品（81%）含有至少 30%的重要肿瘤百分比，从中可以至少 91%分离 500ng DNA。根据我们的预设标准，74%的样品质量足以用于生物标志物的发现。该队列中的 NGS 结果与其他组中的结果一致。用于发现生物标志物以实现个体化癌症治疗的图像引导活检程序是安全可行的，该程序还产生了极具价值的生物样品库。The Oncologist 2017; 22:33-40 Implications for Practice：这项研究表明，执行图像引导活检程序以获得新鲜冷冻肿瘤的样品是安全的，并且在荷兰多中心合作中使用这些活检用于发现生物标志物的目的是可行的。从大多数样品中，可以获得足够的 DNA 来进行新一代测序。这些结果表明已经为未来联盟收集新鲜冷冻肿瘤组织做好了准备。



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Featured Article

文献精读

本期的文献精选是一篇专业文章《对在子宫内膜癌的研究中所使用的生物样品库的标准的协调》。文章的重点在于对现行的多种标准进行协调，从而达成大家普遍接受的版本。癌症研究是一个非常广阔的领域，用于数据收集和分析的手段也多种多样。生物样本库所产生的有效性取决于其质量，这显然取决于严格标准在收集生物样本和患者特征方面的使用，而不同生物样本和伴随的表型和人口统计数据相关的变化使得极其难以推断或整合来自不同研究的数据。权威机构认为，缺乏质量标准和统一性是癌症研究的严重问题。这篇文章所采用的对标准进行协调的方法，为解决这个问题提供了有效途径。

对在子宫内膜癌的研究中所使用的生物样品库的标准的协调

摘要

背景：子宫内膜癌是最常见的妇科癌症，预计其发病率到 2025 年将上升 50-100%，相关死亡率也将相应增加。生物学样本的收集、处理和储存过程是否一致会影响到科学数据的普遍性。本文旨在协调与子宫内膜癌相关的生物样本以及临床数据的收集，并制定收集、处理和储存子宫内膜癌生物样本的标准操作程序。

方法：我们设计了通过三个共识轮次进行评估和修订的研究工具，以获得地方/区域、国家和欧洲的共识。修改的最终工具被传播给代表子宫内膜癌研究的所有利益相关者的小组（n=40），以达成共识。

结果：最终的共识表明与最小的手术和患者数据收集工具的一致统一。另外还有其他标准工具的高度一致意见。

结论：我们在这里介绍了所有子宫内膜癌研究人员可以免费使用的工具的最终版本。我们认为，这些工具将促进子宫内膜癌研究的快速发展，无论是在未来的合作还是大规模的多中心研究中。

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作者：M Adishesh, AFyson, S B DeCruze, J Kirwan, ENITEC Consortium, H M J Wernerand D K Hapangama

背景介绍

子宫内膜癌（EC）是发达国家女性生殖道最常见的癌症，是乳腺癌、肺癌和结肠直肠癌后女性第四大常见癌症（Ferlay 等，2015）。在 2014 年，英国每天至少有 6 名妇女死于子宫内膜癌，同时有 21 名妇女被诊断患有子宫内膜癌。欧共体每年有 9022 例新发病例和 2166 例死亡病例（CRUK）。EC 的发病率迅速增加，预计到 2025 年将增加 50-100%（Lindemann 等，2010）。这种发病率的上升令人震惊，特别是由于死亡率相应上升（CRUK）。因此迫切需要更多地努力寻找新的预防、诊断、预后和治疗目标，以降低与欧共体相关的高死亡率和发病率。传统上，使用基于福尔马林固定石蜡包埋组织的免疫组织化学，仅允许同时研究有限数量的蛋白质。虽然其他细胞系和动物研究已被应用于欧共体研究，但是这些很少提供体内人体环境的完美模拟。因此，收集广泛

的不同患者标本（包括例如新鲜的冷冻组织、尿液、血液或唾液）的生物样品库在为临床相关科学发现提供有价值的患者材料方面起着至关重要的作用，也有助于快速翻译基础科学发现临床实践。

通过其特殊性质，存储在生物样本中的患者材料使研究EC的多个方面成为可能。随着基因组学、蛋白质组学、表观基因组学和代谢组学等新技术平台的出现，这些技术平台可以统一并同时应用于相同的患者样本，以获得最大限度的信息，这一点至关重要。预期这种全面的方法将大大减少新的基础科学发现以新的治疗方式接触患者所花费的时间，并允许患者捐赠的样品被充分利用。

生物样品库所产生的数据的内部和外部的有效性取决于其质量，这显然取决于严格标准在收集生物样本和患者特征方面的使用。与收集、处理、存储不同生物样本和伴随的表型和人口统计数据相关的变化使得极其难以推断或合并来自不同研究的数据（Tworoger 和 Hankinson，2006；Ransohoff 和 Gourlay，2010）。国家癌症研究所（NCI）认为缺乏质量标准和统一性是癌症研究的障碍（NCI 最佳实践，2011 年生物世界资源）。标本和数据收集中的不规则性和不相似性所引起的不可逆转的偏见得到许多人的认可，许多国际组织和机构正在努力克服这一点（Morente 等人，2007 年；国际生物与环境储存学会，2008 年；Yuille 等，2008；Vaught and Lockhart，2012）。

鼓励优化可用于癌症研究的资源的生物样品库 NCI 最佳实践指南（NCI Best Practices for Biospecimen Resources，2011 年，2016 年）广泛提及与捐赠者或样本收集/处理相关的预分析变量的有限列表。从而有效提高了涉及生物样本的研究的整体意识和质量。

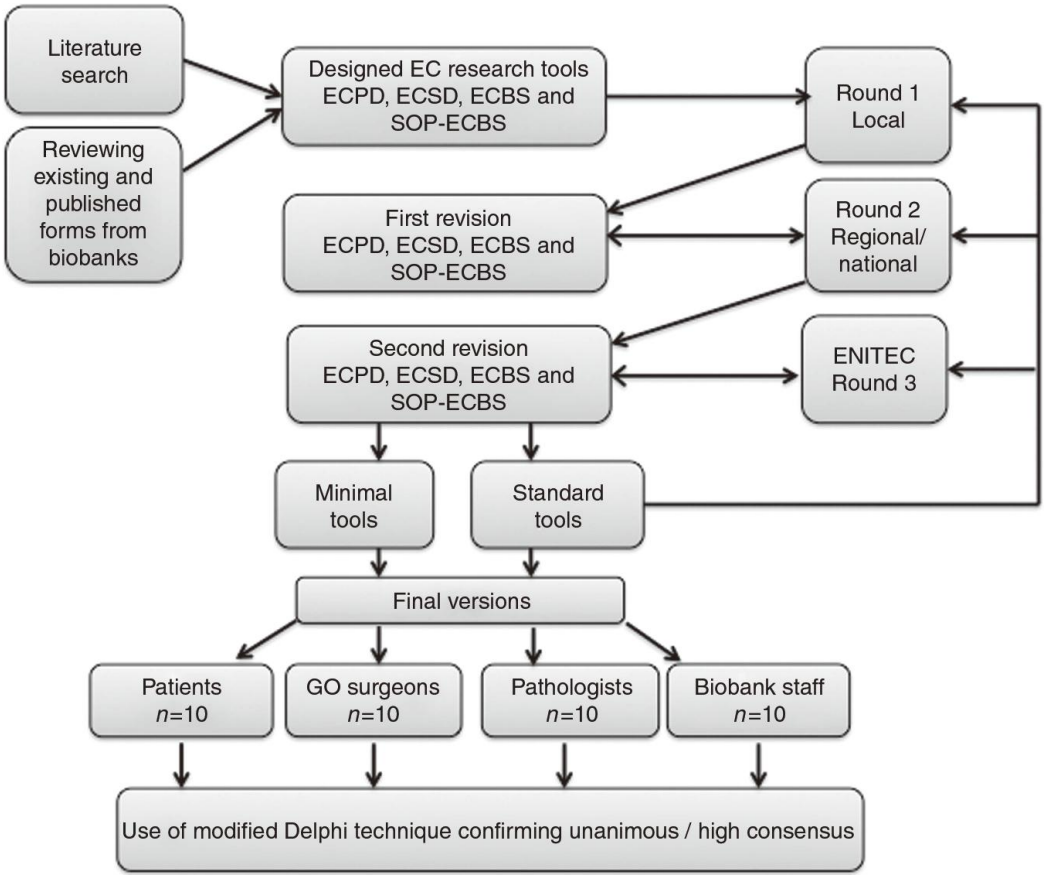

图 1. 流程图，说明了我们在设计 EC 研究工具和产生共识的方法 [子宫内膜癌（EC），欧洲子宫内膜癌个体化治疗网络（ENITEC）]，子宫内膜癌患者数据收集工具（ECPD），子宫内膜癌症手术数据收集工具（ECSD），子宫内膜癌生物手段工具（ECBS），用于 EC 研究（SOP-ECBS）的组织和液体的收集，加工和储存的标准操作程序。

虽然这是一个重要的开始，但许多参数和变量，包括生物样本和临床数据的选择，都是癌症型特异性的。因此，普遍的生物网络化标准不一定适用于每种癌症类型，并且应适应于每种特定疾病。癌症基因组图谱（Kandoth 等，2013）强调了癌症特异性协调生物样品库行业标准的重要性，该基因组图谱现在包含超过 532 个具有 RNA 测序、拷贝数变异、蛋白质组学、突变和微阵列数据的 ECO 样品。然而，这些样本和数据集中大部分的临床数据非常有限，严重影响了研究人员绘制临床适用信息的能力。

因此，EC 特异性标准化采集具有独特和相关的临床数据集的生物样本是改善未来 EC 研究的根本未满足的需求。我们相信，这将有助于未来对 EC 的大规模国际合作研究，这可能导致改进的生物标志物和靶标治疗发现。子宫内膜异位症——世界子宫内膜异位症研究基金会子宫内膜异位症和生物样品库协调项目和卵巢癌研究计划（Wiegand 等，2010；Heravi-Moussavi 等，2012；Fassbender 等，2014；Rahmioglu 等，2014；Vitonis 等，2014）。

有了这个背景，我们开始研究（Harmanization of biobAnking Standards in Endometrial caNcer research-HASTEN），以达成 EC 研究人员的共识、规范所有相关生物样本的收集、处理和储存、以及通过与患者、外科医生/医师/病理学家和生物工程人员的共同努力进行 EC 研究的随附临床数据。我们旨在制定标准——标准操作程序工具，最小和标准数据集将定期更新，并普遍适用于 EC 的未来研究人员。

材料和方法

流程图总结了用于设计 HASTEN 中最终工具的方法（图 1）。我们使用修改后的德尔福系统来分析和确认最终的共识。

表 1. ECPD 工具使用 5 点 Likert 量表的最终一致意见的结果

		Percentages of responses (%)				
Statements in the score sheet for patients	**Score, median (IQR)**	**Strongly agree**	**Agree**	**Undecided**	**Disagree**	**Strongly disagree**
The information asked in personal history is easy to fill	1 (1-2)	60	40	0	0	0
The questions in medical history section are easy to understand and fill	1 (1-2)	60	40	0	0	0
The questions in past history are easy to understand and fill	1 (1-2)	60	40	0	0	0
The questions in social history section are easy to understand and fill	1 (1-2)	60	30	10	0	0
Overall, the form is easy to understand and does not take much time to fill it	1.5 (1-2)	50	50	0	0	0

Abbreviations: ECPD=Endometrial Cancer Patient Data; IQR=interquartile range. IQR, five-point Likert scale: Strongly agree, Agree, Undecided, Disagree and Strongly disagree; n=10.

表 2. ECPD 工具的最终一致意见的结果使用九点李克特量表

		Percentages of responses (%)								
Questions in the score sheet for gynaeoncologists	**Score, median (IQR)**	**Strongly agree**	**Agree**	**Moderately agree**	**Mildly agree**	**Undecided**	**Mildly disagree**	**Moderately disagree**	**Disagree**	**Strongly disagree**
Is the general information about patient relevant?	2 (1.75-2)	20	80	0	0	0	0	0	0	0
Is the section on history relevant?	2 (2-3)	10	60	20	0	0	0	0	10	0
Are the Imaging details relevant and sufficient?	2 (2-4)	10	80	0	30	0	0	0	0	0
Are Antecedent biopsy details relevant?	2 (2-2)	10	80	0	0	0	0	0	0	10
Is the Operative findings section relevant?	2 (1.75-2)	20	80	0	0	0	0	0	0	0
Is the Histopathology type details section relevant and sufficient?	2 (1.75-2.25)	20	60	10	10	0	0	0	0	0
Is the Sample collection details section easy to complete?	2 (1-2)	40	50	0	0	0	0	0	0	10
Are Outcome details relevant?	2 (1.75-2.25)	20	60	10	10	0	0	0	0	0

Abbreviations: ECSD=Endometrial Cancer Surgical Data; IQR=interquartile range. IQR, nine-point Likert scale: Strongly agree, Agree, Moderately agree, Mildly agree, Undecided, Mildly disagree, Disagree and Strongly disagree; n=10.

我们的生成初始工具的过程起始于文献检索。我们使用关键词“子宫内膜癌”、“危险因素”、“介绍年龄”、“平等”、“绝经状态”、“二甲双胍”、“孕激素或曼月乐”、“激素替代疗法”、“多囊卵巢综合征”、“他莫昔芬”、“肠癌”、“结肠直肠癌”、“乳腺癌”、“糖尿病”、“高血压”、“种族”、“人体测评”、“吸烟”、“子宫内膜”、“血液或血浆或血清”、“唾液”、“尿”、“子宫内膜液”、“腹膜液”、“生物样品库最佳实践”、“组织病理学标志物”、“结果”、“组织、血液和体液的实验室处理程序”、“生物分类标准”、“收集组织、液体、血液、唾液、尿液的 SOP”，用以上的关键词搜索了 Scopus，Discover 和 PubMed 数据库。文献搜索仅限于过去 10 年发表的研究。在初步搜索中确定的 3464 篇论文中，根据以下纳入标准，选择了 413 篇文章进行进一步的详细审查：

1. 调查上述因素如何影响个人发展 EC 风险的论文；
2. 提出标准操作程序（SOP）或收集，储存和加工不同组织或液体的最佳做法的出版物；
3. 只有英文的论文；
4. 可通过所有可用资源向作者提供论文（例如，利物浦妇女医院（LWH），利物浦大学，英国医学协会或皇家妇产科学院的在线资源或图书馆设施。

我们进一步对这些选定论文中引用的相关手稿进行手动搜索，并从大型生物解毒剂中进行相关指导。

工具的进一步开发

首次当地咨询。利物浦的当地团队由四名外科妇科肿瘤学小组成员、四名麦克米伦临床癌症护士专家、两名对 EC 研究感兴趣的临床学者、两名病理学家、两名生物工作人员和一名医学生组成，开发出三种形式患者数据收集工具、手术数据收集工具、生物样本表格和标准手术程序。这些形式和 SOP 基于：（a）文献搜索中收集的信息；（b）由 LWH /利物浦大学生物样品库中已经使用的形式，用于收集 EC 研究中的生物样

本和数据。利物浦妇女医院是妇科癌症的高等转诊区域癌症中心，是柴郡和默西塞德战略临床网络的一部分，为 240 万人口提供服务。默西塞德郡和柴郡癌症网络的 EC 年龄标准化发病率为 18.3/10 万女性成员（NCIN，2013；Gynae Clinical Network Constitution，2014-2015）；（c）由国立卫生研究院，人子宫内膜组织和 DNA 银行开发的用于收集、运输和储存子宫内膜组织和进行子宫内膜活检或子宫切除术的非恶性指征的女性血液样本的标准操作程序（Sheldon 等，2011）；（d）英国生物库公布的收集尿液和血液样本的样品处理和储存方案（Elliott 等，2008）。英国生物样品库是维康信托、医学研究理事会、卫生部、苏格兰政府和西北地区发展局成立的国家和国际重要卫生资源，其主要目的是改善癌症、心脏病、中风、糖尿病、关节炎、骨质疏松症和痴呆等许多疾病的预防、诊断和治疗。

第二次区域/国家磋商。上述三种形式的修改版本和上述 SOP 在联合国参与欧共体研究的三个区域和八个国家研究中心之间传播，形式修订整合了其反馈，结果是两种不同的工具，一种是最小的和一种开发了标准的工具。这种务实和包容性的方法为考虑可用资源收集最小或理想的“标准”数据集提供了指导。

第三次欧洲咨询。然后将修改后的表格分发给所有坚持欧洲子宫内膜癌个性化治疗网络（ENITEC）的研究人员，并根据收到的反馈进一步修订。修订的工具在 2016 年 6 月的年度 ENITEC 面对面会议上提出，最小形式得到所有 47 名与会者的一致通过。对标准工具进行了一些进一步修改，并作了相应修订，修订后的表格重新填补了所有参加第 1-3 次磋商的情况，得到最后的批准。

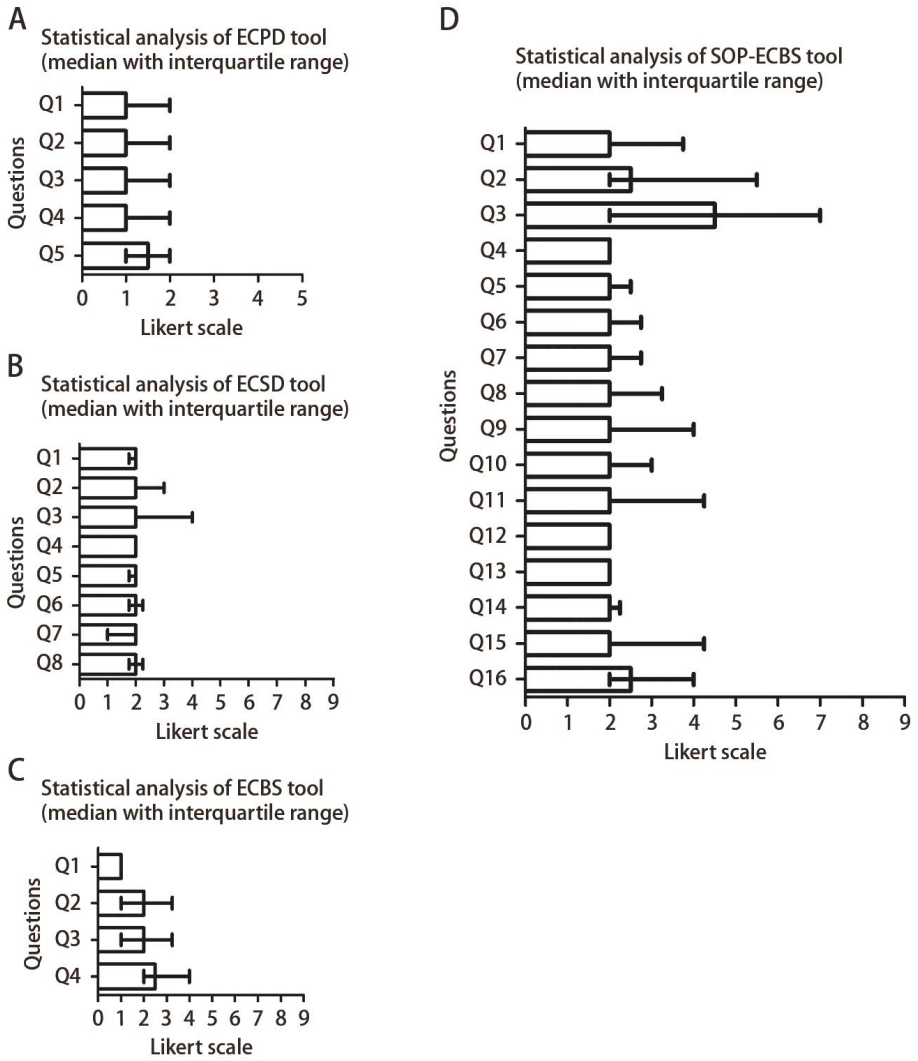

图 2. 子宫内膜癌患者数据收集工具（ECPD），子宫内膜癌手术数据收集工具（ECSD），子宫内膜癌生物手段工具（ECBS）和 EC 研究组织和液体收集、加工和储存的标准操作程序的统计分析（SOP-ECBS）工具。

达成共识。共识一代修改后的 Delphi 系统被用于对最终的修改工具产生共识。为此，将这些表格传播给代表所有前几轮所有利益相关者的一组选定小组成员，包括患者、妇科肿瘤学家、研究人员、病理学家和生物工作人员，从咨询参与者（n=40）中随机选择使用记录他们的协议的评分表评估和评分工具。

统计分析。使用修改的德尔菲技术对共识进行了量化，我们已经报告了中位数为四分位数范围，并且还有 Likert 量表的每个类别的百分比。使用了九分李克特量表，除了患者数据工具，其量表减少到五点，以减少患者的复杂性。

结果

本研究的最终工具是 ECPD 收集工具。我们设计了一种耐心友好的数据收集工具 [EC 患者数据（ECPD）] 来捕获与 EC 研究直接相关的许多重要人口统计学变量，只能由患者自己准确回忆。例如，现有的文献表明 420 kg 与 EC 增加风险独立相关的成人体重增加（Friedenreich 等，2007）并且这种信息不可能直接从患者身上获得。EC 的许多其他危险因素，如年龄、绝经后状态、多囊性卵巢疾病（Fearnley 等，2010）、无效性（Schonfeld 等，2013）、月经初潮（Gong 等，2015）、家庭遗传性疾病综合征性癌症的历史（Boilesen 等人，2008）、过去的疾病综合征相关癌症病史、糖尿病等医学病症（Friberg 等，2007）、先前使用他莫昔芬（Bergman 等，2000）、激素替代疗法使用（Beral 等，2005 年）和运动习惯已被纳入该工具。目前还有一些其他因素与目前的 EC（Lindemann 等人，2008）没有任何联系，因为他们在今后的研究中肯定了这一点。表 1 和图 2 说明了最后一轮协商一致的结果。

ECPD 中每个问题的得分使用 Likert 量表获得，Likert 量表评估可接受性和可用性（n=10）。在小组成员中，只有 2% 在社会历史部分的问题清晰度方面未定，总共 98% 的患者同意该工具易于使用。

表 3. ECBS 工具使用九分李克特量表的最终一致意见的结果

		Percentages of responses (%)								
Questions in the score sheet for biobank staff	**Score Median (IQR)**	**Strongly agree**	**Agree**	**Moderately agree**	**Mildly agree**	**Undecided**	**Mildly disagree**	**Moderately disagree**	**Disagree**	**Strongly disagree**
Sample ID–Is this relevant?	1 (1-1)	90	10	0	0	0	0	0	0	0
Methods of tissue processing (Endometrium)–Is this section easy to understand?	2 (1-3.25)	40	30	10	10	0	0	0	10	0
Methods of tissue processing (Extra uterine tissue)–Is this section easy to understand?	2 (1-3.25)	40	30	10	10	0	0	0	10	0
Methods of fluid processing (Endometrial/Peritoneal/ Blood/Saliva/Urine)–Is this section easy to understand?	2.5 (2-4)	10	40	10	40	0	0	0	0	0

Abbreviations: ECBS=Endometrial Cancer Biospecimen; IQR=interquartile range. IQR, nine-point Likert scale: Strongly agree, Agree, Moderately agree, Mildly agree, Undecided, Mildlydisagree, Disagree and Strongly disagree; n=10

ECSD 收集工具。EC 手术数据（ECSD）工具包括突出的人口统计学、组织学和术前/术后特征。包括人体特征如体重指数（BMI）。选择身体质量指数代替腰臀比或腰围，因为其普遍使用和重现性。尽管所有人体测量（BMI，腰臀比，腰围和臀围周围）都被发现与 EC 风险增加密切相关（Friedenreich 等，2007），腰臀比或腰围的准确数据需要额外的努力来使用医疗团队相同的参考点，因此准确的数据收集不可能普遍可行。在最近的一项研究（Painter 等，2016）中，BMI 被发现是一个因素，与 EC 和腰臀比相关。术前成像细节有助于评估局部扩散和排除远处转移。子宫内膜活检和最终组织学结果之间的差异已被证明与较差的生存结果相关（Werner 等，2013）。因此，术前活检结果很重要。与结果相关时，手术后的分期细节，包括手术结果和最终组织病理学细节是重要的。免疫组织化学生物标志物可用于区分卵巢癌，子宫颈癌或其他恶性肿瘤，但重要的是与临床预后相关的预后生物标志物（Li 等，2013；Kamal 等，2016）。以标准方式与生物样本一起收集的信息自然会增加生成数据的内部和外部有效性。应定期更新患者资料，包括随访和准确记录死亡原因，直至完成标准随访期（3 年（至少）或 5 年，视当地实践而定）。表格分为三个部分：

（1）手术资料：收集样本时完成；

（2）组织病理学细节：最终分期治疗后完成；

（3）在随访期间记录，最后在随访结束时记录。

最终共识的结果如表 2 和图 2 所示，其中我们用四分位数范围计算了中位数。所有小组的小组成员之间达成了高度的一致意见，但一些答复者认为有关历史，先前活检细节和样本收集细节的部分不相关。总体来说，96.25%的小组成员同意该工具的不同方面（补充图 S1）。

EC 生物样本工具。收集方法和生物样品库条件（处理和储存）的变化可能改变生物标志物分布的分子组成、表达和稳定性（Zander 等，2014）。因此，一致性和严格遵守标准操作程序至关重要（Moore 等，2011）。因此，具有临床生物样品库应用经验和知识的生物工作人员参与了生物样本形式的设计、修订和获得最终共识。只有少数受访者认为形式的组织处理（子宫和宫外）部分难以理解，而所有受访者都同意所有其他部分的相关性和清晰度。总体来说，这个工具的不同方面达成了 94%的协议。详细结果如表 3，图 2 和补充图 S1 所示。

用于 EC 研究的组织和液体的收集、加工和储存的标准操作程序。EC 研究中研究了不同组织类型（子宫和宫外）和体液类型。这些生物样本的常规研究可能涉及使用蛋白质组学、基因组学和代谢组学等多种技术提取待评估的蛋白质、RNA 和 DNA。最终的 SOP 设计合并了许多可用的单独的详细方法方案（例如，用于离心、过滤、添加防腐剂以及储存温度）。从生物样品库获得这些信息将使科学家能够准确地解读其数据，例如检查血液、组织、子宫内膜液或抽吸物等样品的代谢特征，并自信地检测疾病特异性变化，特别是在多中心研究中（Assfalg 等，2008；Bernini 等，2009）。检查激素的研究与子宫内膜有重要关系，除了传统的血液样本之外，还有一些研究人员研究了非侵入性标本，包括唾液和尿液（Shirtcliff 等，2001）。非侵入性测试对临床研究特别有兴趣，未来工作预计将更多地集中在他们身上。

关于用于 EC 研究（SOP-ECBS）的组织和液体的收集、处理和储存的标准操作程序的最终一致意见的结果细节如表 4 和图 2 所示。关于用户的一般性协议友好和工具的相关性，少数小组成员回答说，为了清楚起见，可以进一步修改组织和血液收集细节。总体上，83.75%的小组成员同意，8.75%未定，7.5%不同意这一工具的不同部分。

讨论

我们已经开发了以证据为基础的标准数据收集表格 ECPD、ECSD（最小）、ECSD（标准）和 SOP-ECBS，包括所有利益相关者在 EC 癌症生物样品库中的参与和批准。最终的工具被一个大型的多学科评审小组批准，达成一致后（见补充图 S1），它们作为补充信息公布在这个开放存取手稿中。因此，他们将免费向国际上所有的欧盟研究人员提供。这些工具提供了一种减少收集数据中的混杂因素并促进更大型多中心研究的方法。

我们选择要收集的确切信息是基于对最佳现有证据的批判性评估。没有公开证据的地方，考虑了专家意见和较大生物样品库的 SOPs 的咨询。处理血液的离心速度就是这样一个例子。

我们使用了一种修改后的德尔菲技术，该标准技术具有多项改进，包括多轮反馈，允许相同的小组成员重新评估或重新考虑初步判断、参与者匿名、受控反馈和统计分析以解释轮次之间的数据。以前已经使用了与原始德尔福系统相似的变化，例如限制专家对专家组的原始问题和变更的响应能力以及改变终点的能力（Thompson，2009）。

对于我们的研究目的，反复使用同质小组是不合理的，原因如下。我们的努力是为不同的终点产生单独的形式，例如患者数据收集、手术数据收集、组织处理信息和标准手术程序。这些明显需要不同背景的小组成员和具有不同的专业领域，因此我们的小组成员不是一个同质的组织。

表 4. SOP-ECBS 工具使用九点李克特量表的最终一致意见的结果

		Percentages of responses (%)								
Questions in the score sheet for pathologists	**Score Median (IQR)**	**Strongly agree**	**Agree**	**Moderately agree**	**Mildly agree**	**Undecided**	**Mildly disagree**	**Moderately disagree**	**Disagree**	**Strongly disagree**
Is section: Processing and storage materials, relevant and easy to understand?	2 (2-3.75)	10	50	20	0	0	20	0	0	0
Is section: Collection–Tissue, relevant and easy to understand?	2.5 (2-5.5)	10	40	10	10	10	0	20	0	0
Is section: Collection–Blood, relevant and easy to understand?	4.5 (2-7)	10	30	0	10	10	10	30	0	0
Is section: Collection – Urine, relevant and easy to understand?	2 (2-2)	10	80	10	0	0	0	0	0	0
Is section: Collection – Saliva, relevant and easy to understand?	2 (2-2.5)	10	70	0	10	10	0	0	0	0
Is section: Collection – Peritoneal fluid, relevant and easy to understand?	2 (2-2.75)	0	80	0	0	20	0	0	0	0
Is section: Collection – Endometrial fluid/uterine aspirates, relevant and easy to understand?	2 (2-2.75)	0	80	0	0	20	0	0	0	0
Is section: Sample processing – Tissue, relevant and easy to understand?	2 (2-3.25)	0	70	10	10	10	0	0	0	0
Is section: Sample processing – Blood, relevant and easy to understand?	2 (2-4)	0	60	10	20	10	0	0	0	0
Is section: Sample processing – Urine, relevant and easy to understand?	2 (2-3)	0	70	20	0	0	10	0	0	0
Is section: Sample processing – Saliva, relevant and easy to understand?	2 (2-4.25)	0	60	10	10	10	10	0	0	0
Is section: Sample processing – Peritoneal fluid, relevant and easy to understand?	2 (2-2)	10	80	0	0	10	0	0	0	0
Is section: Sample processing – Endometrial fluid/uterine aspirates, relevant and easy to understand?	2 (2-2)	10	80	0	0	10	0	0	0	0
Is section: Storage and data recording, relevant and easy to understand?	2 (2-2.25)	10	70	10	0	0	10	0	0	0
Is section: Freezer check, relevant and easy to understand?	2 (2-4.25)	0	60	10	10	10	10	0	0	0
Is section: Checklist, relevant and easy to understand?	2.5 (2-4)	0	50	10	30	10	0	0	0	0

Abbreviations: IQR=interquartile range; SOP-ECBS=standard operating procedure for collection, processing and storage of tissue and fluid for EC research. IQR, nine-point Likert scale: Strongly agree, Agree, Moderately agree, Mildly agree, Undecided, Mildly disagree, Disagree and Strongly disagree; n=10.

与经典技术的主要偏差是咨询轮次数和终点数。我们的前两轮是描述性的，以产生不同专家组的意见和想法。我们通过他们的反馈，以产生最终的表格和 SOP。在最后一轮的协商一致意见中，我们向每个小组成员分发了一张表格，并附上表格，评估他们与最终工具的协议。我们的最后一个小组包括所有以前小组参与的利益相关者。通过对从第三轮和最后一轮获得的数据的统计分析观察到的高比例的协议排除了进一步的共识轮回的需要。

更详细的是，标准化的手术数据收集将可以全面评估外科表型数据与治疗结果之间的关系，我们强烈建议使用标准而不是最小的 ECSD 工具。但是，如果无法保证大量数据或样本的收集或质量，则应采用最小集合。我们计划通过反馈和未来文献综述获取信息，定期更新这些工具，最初是每年 5 年，之后 3 年。在我们的举措范围内的未来考虑包括建立一个国际资助的基于网络的中央数据库系统，允许自愿将信息存储在全球范围内的欧洲研究组织研究人员收集的所有生物样本信息中。我们认为，这种方法可以降低各个单位的成本和时间，同时增加生成的数据的可信度，并为更新的协作提供一个透明的通用平台。

“分子病理流行病学”（MPE）整合了病理学和流行病学，以了解影响癌症发生，进展和治疗反应的外源性和内源性因素之间的相互关系。它是癌症研究中不断发展的领域（Ogino 和 Stampfer，2010）。还开发了统计学方法来考虑分子病理学和流行病学，以确保具有高临床影响的新发现。然而，与传统的分子生物学研究（Hughes 等，2012；Campbell 等，2017）相似的类似挑战，包括选择和回忆偏倚、测量误差和错误分类，这些高度影响的 MPE 研究的产生受到阻碍。组织检索率和样本量的变异性导致随机和非随机选择偏倚，导致效应估计与宽置信区间和出版偏倚的巨大差异（Ogino 等，2011）。EC 生物库使用我们的工具将提供一种手段，简化从表型良好的患者中收集大量标准化的质量保证材料。这将反过来促进充分动力的研究，提供高临床影响，同时也促进在可接受的时间范围内可达到的高质量研究。

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利益冲突

作者宣称没有利益冲突。

参考文献

1. Assfalg M, Bertini I, Colangiuli D, Luchinat C, Scha¨fer H, Schu¨tz B, Spraul M
2. (2008) Evidence of different metabolic phenotypes in humans. Proc Natl AcadSci USA 105(5): 1420–1424.
3. Beral V, Bull D, Reeves G, Collaborators MWS (2005) Endometrial cancer and hormone-replacement therapy in the Million Women Study. Lancet 365(9470): 1543–1551.
4. Bergman L, Beelen ML, Gallee MP, Hollema H, Benraadt J, van Leeuwen FE (2000) Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of Liver and Endometrial cancer Risk following Tamoxifen. Lancet 356(9233): 881–887.
5. Bernini P, Bertini I, Luchinat C, Nepi S, Saccenti E, Scha¨fer H, Schu¨tz B, Spraul M, Tenori L (2009) Individual human phenotypes in metabolic space and time. J Proteome Res 8(9): 4264–4271.
6. Boilesen AE, Bisgaard ML, Bernstein I (2008) Risk of gynecologic cancers in Danish hereditary non-polyposis colorectal cancer families. Acta Obstet Gynecol Scand 87(11): 1129–1135.
7. Campbell PT, Rebbeck TR, Nishihara R, Beck AH, Begg CB, Bogdanov AA, Cao Y, Coleman HG, Freeman GJ, Heng YJ, Huttenhower C, Irizarry RA, Kip NS, Michor F, Nevo D, Peters U, Phipps AI, Poole EM, Qian ZR, Quackenbush J, Robins H, Rogan PK, Slattery ML, Smith-Warner SA, Song M, Vander Weele TJ, Xia D, Zabor EC, Zhang X, Wang M, Ogino S(2017) Proceedings of the third international molecular pathological epidemiology (MPE) meeting. Cancer Causes Control 28(2): 167–176.
8. CRUK. Uterine Cancer Statistics, Vol. 2015. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statisticsby-cancer-type/uterine-cancer.
9. Elliott P, Peakman TC, Biobank U (2008) The UK Biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine.Int J Epidemiol 37(2): 234–244.
10. Fassbender A, Rahmioglu N, Vitonis AF, Vigano P, Giudice LC, D'Hooghe TM, Hummelshoj L, Adamson GD, Becker CM, Missmer SA, Zondervan KT, Group WEW (2014) World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project: IV. Tissue collection, processing, and storage in endometriosis research. Fertil Steril 102(5): 1244–1253.
11. Fearnley EJ, Marquart L, Spurdle AB, Weinstein P, Webb PM, Australian Ovarian Cancer Study Group and Australian National Endometrial Cancer Study Group (2010) Polycystic ovary syndrome increases the risk of endometrial cancer in women aged less than 50 years: an Australian case–control study. Cancer Causes Control 21(12): 2303–2308.
12. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 136(5): E359–E386.

13. Friberg E, Orsini N, Mantzoros CS, Wolk A (2007) Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia 50(7): 1365–1374.

14. Friedenreich C, Cust A, Lahmann PH, Steindorf K, Boutron-Ruault MC, Clavel-Chapelon F, Mesrine S, Linseisen J, Rohrmann S, Boeing H, Pischon T, Tjønneland A, Halkjaer J, Overvad K, Mendez M, Redondo ML, Garcia CM, Larran˜aga N, Tormo MJ, Gurrea AB, Bingham S, Khaw KT, Allen N, Key T, Trichopoulou A, Vasilopoulou E, Trichopoulos D, Pala V, Palli D, Tumino R, Mattiello A, Vineis P, Bueno-de-Mesquita HB, Peeters PH, Berglund G, Manjer J, Lundin E, Lukanova A, Slimani N, Jenab M, Kaaks R, Riboli E (2007) Anthropometric factors and risk of endometrial cancer: the European prospective investigation into cancer and nutrition. Cancer Causes Control 18(4): 399–413.

15. Gong TT, Wang YL, Ma XX (2015) Age at menarche and endometrial cancer risk: a dose-response meta-analysis of prospective studies. Sci Rep 5: 14051.

16. Gynae Clinical Network Constitution (2014–2015) Available at: http://www.nwcscnsenate.nhs.uk/files/2314/1172/3867/Gynae_CNG_Constitution_ 2014.pdf.

17. Heravi-Moussavi A, Anglesio MS, Cheng SW, Senz J, Yang W, Prentice L, Fejes AP, Chow C, Tone A, Kalloger SE, Hamel N, Roth A, Ha G, Wan AN, Maines-Bandiera S, Salamanca C, Pasini B, Clarke BA, Lee AF, Lee CH, Zhao C, Young RH, Aparicio SA, Sorensen PH, Woo MM, Boyd N, Jones SJ, Hirst M, Marra MA, Gilks B, Shah SP, Foulkes WD, Morin GB, Huntsman DG (2012) Recurrent somatic DICER1 mutations in nonepithelial ovarian cancers. N Engl J Med 366(3): 234–242.

18. Hughes LA, Williamson EJ, van Engeland M, Jenkins MA, Giles GG, Hopper JL, Southey MC, Young JP, Buchanan DD, Walsh MD, van den Brandt PA, Alexandra Goldbohm R, Weijenberg MP, English DR (2012) Body size and risk for colorectal cancers showing BRAF mutations or microsatellite instability: a pooled analysis. Int J Epidemiol 41(4): 1060–1072.

19. International Society for Biological and Environmental Repositories (2008) Best Practices for Respositories: Collection, Storage, Retrieval and Distribution of Biological Materials for Research. In Cell preservation technology, Vol 6, 2nd edition. Mary Ann Liebert, Inc.: New Rochelle, NY, USA.

20. Kamal A, Tempest N, Parkes C, Alnafakh R, Makrydima S, Adishesh M, Hapangama DK (2016) Hormones and endometrial carcinogenesis. Horm Mol Biol Clin Invest 25(2): 129–148.

21. Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, Robertson AG, Pashtan I, Shen R, Benz CC, Yau C, Laird PW, Ding L, Zhang W, Mills GB, Kucherlapati R, Mardis ER, Levine DA, Network CGAR (2013) Integrated genomic characterization of endometrial carcinoma. Nature 497(7447): 67–73.

22. Li MZL, Qi W, Shen D, Li X, Wang J, Wei L (2013) Clinical implications and prognostic value of five biomarkers in endometrial carcinoma. Chin-German J Clinl Oncol 12(12): 586–591.

23. Lindemann K, Eskild A, Vatten LJ, Bray F (2010) Endometrial cancer incidence trends in Norway during 1953–2007 and predictions for 2008–2027. Int J Cancer 127(11): 2661–2668.

24. Lindemann K, Vatten LJ, Ellstrøm-Engh M, Eskild A (2008) Body mass, diabetes and smoking, and endometrial cancer risk: a follow-up study. Br J Cancer 98(9): 1582–1585.

25. Moore HM, Kelly A, Jewell SD, Mc Shane LM, Clark DP, Greenspan R, Hainaut P, Hayes DF, Kim P, Mansfield E, Potapova O, Riegman P, Rubinstein Y, Seijo E, Somiari S, Watson P, Weier HU, Zhu C, Vaught J (2011) Biospecimen reporting for improved study quality. Biopreserv Biobank 9(1): 57–70.

26. Morente MM, de Alava E, Fernandez PL (2007) Tumour banking: the Spanish design. Pathobiology 74(4): 245–250. National Cancer Institute (2011) Best Practices For Biospecimen Resources. NIH: Bethesda, MD, USA. Available at: https://biospecimens.cancer.gov/practices/2011bp.asp.

27. National Cancer Institute (2016) Best Practices For Biospecimen Resources. NIH: Bethesda, MD, USA. Available at: https://biospecimens.cancer.gov/bestpractices/2016-NCIBestPractices.pdf.

28. NCIN (2013) Outline of Uterine Cancer in the United Kingdom: Incidence, Mortality and Survival. NCIN. PHE Knowledge and Intelligence Team (East Midlands): Sheffield, UK.

29. Ogino S, Chan AT, Fuchs CS, Giovannucci E (2011) Molecular pathological epidemiology of colorectal neoplasia: an emerging transdisciplinary and interdisciplinary field. Gut 60(3): 397–411.

30. Ogino S, Nishihara R, Vander Weele TJ, Wang M, Nishi A, Lochhead P, Qian ZR, Zhang X, Wu K, Nan H, Yoshida K, Milner Jr DA, Chan AT, Field AE, Camargo Jr CA, Williams MA, Giovannucci EL (2016) Review article: the role of molecular pathological epidemiology in the study of neoplastic and non-neoplastic diseases in the era of precision medicine. Epidemiology 27(4): 602–611.

31. Ogino S, Stampfer M (2010) Lifestyle factors and microsatellite instability in colorectal cancer: the evolving field of molecular pathological epidemiology. J Natl Cancer Inst 102(6): 365–367.

32. Painter JN, O'Mara TA, Marquart L, Webb PM, Attia J, Medland SE, Cheng T, Dennis J, Holliday EG, McEvoy M, Scott RJ, Ahmed S, Healey CS, Shah M, Gorman M, Martin L, Hodgson SV, Beckmann MW, Ekici AB, Fasching PA, Hein A, Ru¨bner M, Czene K, Darabi H, Hall P,Li J, Do¨rk T, Du¨rst M, Hillemanns P, Runnebaum IB, Amant F,Annibali D, Depreeuw J, Lambrechts D, Neven P, Cunningham JM, Dowdy SC, Goode EL, Fridley BL, Winham SJ, Njølstad TS, Salvesen HB, Trovik J, Werner HM, Ashton KA, Otton G, Proietto A, Mints M, Tham E, Bolla MK, Michailidou K, Wang Q, Tyrer JP, Hopper JL, Peto J, Swerdlow AJ, Burwinkel B, Brenner H, Meindl A, Brauch H, Lindblom A, Chang-Claude J, Couch FJ, Giles GG, Kristensen VN, Cox A, Pharoah PD,Tomlinson I, Dunning AM, Easton DF, Thompson DJ, Spurdle AB, Group A, RENDOCAS f, (NSECG) NSoECGG, (ANECS) ANECSG (2016) Genetic risk score Mendelian randomization shows that obesity measured as body mass index, but not waist:hip ratio, is causal for endometrial cancer. Cancer Epidemiol Biomarkers Prev 25(11): 1503–1510.

33. Rahmioglu N, Fassbender A, Vitonis AF, Tworoger SS, Hummelshoj L, D'Hooghe TM, Adamson GD, Giudice LC, Becker CM, Zondervan KT, Missmer SA, Group WEW (2014) World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project: III. Fluid biospecimen collection, processing, and storage in endometriosis research. Ferti lSteril 102(5): 1233–1243.

34. Ransohoff DF, Gourlay ML (2010) Sources of bias in specimens for research about molecular markers for cancer. J ClinOncol 28(4): 698–704.

35. Schonfeld SJ, Hartge P, Pfeiffer RM, Freedman DM, Greenlee RT, Linet MS, Park Y, Schairer C, Visvanathan K, Lacey JV (2013) An aggregated analysis of hormonal factors and endometrial cancer risk by parity. Cancer 119(7): 1393–1401.

36. Sheldon E, Vo KC, McIntire RA, Aghajanova L, Zelenko Z, Irwin JC, Giudice LC (2011) Biobanking human endometrial tissue and blood specimens: standard operating procedure and importance to reproductive biology research and diagnostic development. FertilSteril 95(6): 2120–2122. e1–e12.

37. Shirtcliff EA, Granger DA, Schwartz E, Curran MJ (2001) Use of salivary biomarkers in biobehavioral research: cotton-based sample collection methods can interfere with salivary immunoassay results. Psychoneuroendocrinology 26(2): 165–173.

38. Thompson M (2009) Considering the implication of variations within Delphi research. FamPract 26(5): 420–424.

39. Tworoger SS, Hankinson SE (2006) Use of biomarkers in epidemiologic studies: minimizing the influence of measurement error in the study design and analysis. Cancer Causes Control 17(7): 889–899.

40. Vaught J, Lockhart NC (2012) The evolution of biobanking best practices. ClinChimActa 413(19-20): 1569–1575.

41. Vitonis AF, Vincent K, Rahmioglu N, Fassbender A, Buck Louis GM, Hummelshoj L, Giudice LC, Stratton P, Adamson GD, Becker CM, Zondervan KT, Missmer SA, Group WEW (2014) World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project: II. Clinical and covariate phenotype data collection in endometriosis research. Fertil Steril 102(5): 1223–1232.

42. Werner HMJ, Trovik J, Marcickiewicz J, Tingulstad S, Staff AC, Engh ME, Oddenes K, Rokne JA, Tjugum J, Lode MS, Amant F, Salvesen HB (2013) A discordant histological risk classification in preoperative and operative biopsy in endometrial cancer is reflected in metastatic risk and prognosis. Eur J Cancer 49: 625–632.

43. Wiegand KC, Shah SP, Al-Agha OM, Zhao Y, Tse K, Zeng T, Senz J, McConechy MK, Anglesio MS, Kalloger SE, Yang W, Heravi-Moussavi A, Giuliany R, Chow C, Fee J, Zayed A, Prentice L, Melnyk N, Turashvili G, Delaney AD, Madore J, Yip S, McPherson AW, Ha G, Bell L, Fereday S, Tam A, Galletta L, Tonin PN, Provencher D, Miller D, Jones SJ, Moore RA, Morin GB, Oloumi A, Boyd N, Aparicio SA, Shih IeM, Mes-Masson AM, Bowtell DD, Hirst M, Gilks B, Marra MA, Huntsman DG (2010) ARID1A mutations in endometriosis-associated ovarian carcinomas. N Engl J Med 363(16): 1532–1543.

44. Yuille M, van Ommen GJ, Bre´chot C, Cambon-Thomsen A, Dagher G, Landegren U, Litton JE, Pasterk M, Peltonen L, Taussig M, Wichmann HE, Zatloukal K (2008) Biobanking for Europe. Brief Bioinform 9(1): 14–24.

45. Zander J, Bruegel M, Kleinhempel A, Becker S, Petros S, Kortz L, Dorow J, Kratzsch J, Baber R, Ceglarek U, Thiery J, Teupser D (2014) Effect of biobanking conditions on short-term stability of biomarkers in human serum and plasma. Clin Chem Lab Med 52(5): 629–639.

Harmonisation of biobanking standards in endometrial cancer research

M Adishesh[1,2], A Fyson[2], S B DeCruze[1], J Kirwan[1], ENITEC Consortium, H M J Werner[3,4] and D K Hapangama[*,1,2]

[1]*Liverpool Women's Hospital NHS Foundation Trust, Crown Street, Liverpool L8 7SS, UK;* [2]*Department of Women's and Children's Health, Institute of Translational Medicine, University of Liverpool, Liverpool Women's Hospital, Crown Street, Liverpool L8 7SS, UK;* [3]*Department of Obstetrics and Gynaecology, Haukeland University Hospital, Jonas Liesvei 70, 50503 Bergen, Norway and* [4]*Department of Clinical Science, University of Bergen, Bergen 5021, Norway*

Background: Endometrial cancer is the most common gynaecological cancer and its incidence is predicted to escalate by 50–100% in 2025 with a parallel increase in associated mortality. Variations in the collection, processing and storage of biospecimens can affect the generalisability of the scientific data. We aimed to harmonise the collection of biospecimens, clinical data relevant to endometrial cancer and to develop standard operative procedures for the collection, processing and storage of endometrial cancer biospecimens.

Methods: We designed research tools, which were evaluated and revised through three consensus rounds – to obtain local/regional, national and European consensus. Modified final tools were disseminated to a panel ($n = 40$) representing all stakeholders in endometrial cancer research for consensus generation.

Results: The final consensus demonstrated unanimous agreement with the minimal surgical and patient data collection tools. A high level of agreement was also observed for the other remaining standard tools.

Conclusions: We here present the final versions of the tools, which are freely available and easily accessible to all endometrial cancer researchers. We believe that these tools will facilitate rapid progress in endometrial cancer research, both in future collaborations and in large-scale multicentre studies.

Endometrial cancer (EC) is the most common cancer of the female genital tract in the developed world, and is the fourth most common cancer in women after breast, lung and colorectal cancer (Ferlay *et al*, 2015). In the United Kingdom in 2014, at least 6 women died of and 21 women were diagnosed with EC in the United Kingdom every day, with 9022 new cases and 2166 deaths reported that year (CRUK). The incidence rate of EC is increasing rapidly and is estimated to increase by 50–100% by 2025 (Lindemann *et al*, 2010). This increase in incidence is alarming, particularly due to the corresponding rise in mortality (CRUK). Increased efforts into finding new prevention, diagnostic, prognostic and therapeutic targets are therefore urgently required to reduce the high mortality and morbidity rates associated with EC. Traditionally, among others immunohistochemistry was used, based on formalin-fixed paraffin-embedded tissue, allowing only for the study of a limited number of proteins simultaneously. Further cell lines and animal studies have been applied in EC research; these however rarely give a perfect simulation of the *in vivo* human environment. Therefore, biobanks, collecting a wide range of different patient specimens, including for example fresh frozen tissue, urine, blood or saliva, have a vital role in providing valuable patient material for clinically relevant scientific discoveries and also aid to the rapid translation of basic scientific findings to clinical practice.

Through its nature, patient material stored in biobanks allows for studying multiple aspects of EC. This is of paramount importance with the emergence of novel technological platforms in genomics, proteomics, epigenomics and metabolomics that can be collectively and simultaneously applied to the same patient samples to gain the maximum amount of information. Such an all-

*Correspondence: Dr DK Hapangama; E-mail: dharani@liv.ac.uk

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encompassing approach is expected to reduce considerably the time taken for new basic scientific discoveries to reach patients as new treatments as well as allowing the samples donated by patients to be fully used.

The internal and external validity of the generated data depend on their quality, which is clearly dependent on the use of stringent standards in collecting the biospecimens and patient characteristics. Variations associated with collecting, processing, storing different biospecimens and the accompanying phenotypic and demographic data make it extremely difficult to extrapolate or to merge data from different studies (Tworoger and Hankinson, 2006; Ransohoff and Gourlay, 2010). This lack of quality standards and uniformity is recognised by the National Cancer Institute (NCI) as a roadblock in cancer research (NCI Best Practices for Biospecimen Resources, 2011). The irrevocable bias introduced by the irregularities and dissimilarities in specimens and data collection are well recognised by many and efforts are being made to overcome this by several international organisations and agencies (Morente *et al*, 2007; International Society for Biological and Environmental Repositories, 2008; Yuille *et al*, 2008; Vaught and Lockhart, 2012).

The NCI best practice guidance for biobanks (NCI Best Practices for Biospecimen Resources, 2011, 2016), which encourages optimisation of the resources available for cancer research, broadly mentions a limited list of preanalytic variables related to the donor or sample collection/processing. It has thereby been effective in raising the overall awareness and quality of research involving biospecimens.

Although this is an important start, many parameters and variables of interest, including choice of biospecimens and clinical data, are cancer-type-specific. Thus, universal biobanking standards are not necessarily applicable to every cancer type and should be adapted to each specific disease. The importance of cancer-specific harmonisation of biobanking standards is highlighted by the cancer genome atlas (Kandoth *et al*, 2013), which now contains over 532 EC samples with RNA sequencing, copy number variation, proteomic, mutation and microarray data. However, the extremely limited clinical data accompanying most of these samples and data sets severely affects the ability of researchers to draw clinically applicable information.

Therefore, EC-specific standardisation of the collection of biospecimens with distinctive and relevant accompanying clinical data sets is a fundamental unmet need in improving future EC research. This, we believe, will facilitate future large-scale internationally collaborative research into EC, which could lead to improved biomarker and target treatment discovery. Similar harmonisation projects have already been successfully implemented for other gynaecological conditions such as endometriosis – World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project and Ovarian Cancer Research Program (Wiegand *et al*, 2010; Heravi-Moussavi *et al*, 2012; Fassbender *et al*, 2014; Rahmioglu *et al*, 2014; Vitonis *et al*, 2014).

With this background, we initiated our study (Harmonisation of biobAnking STandards in Endometrial caNcer research – HASTEN) to achieve consensus among EC researchers; standardise the collection, processing and storage of all relevant biospecimens; and the accompanying clinical data for EC research through a joint effort with patients, surgeons/physicians/pathologists and the personnel of biobanks. We aimed to develop standards: standard operative procedure tools with a minimum and standard data set to be regularly updated and universally available for future researchers in EC.

MATERIALS AND METHODS

The method used to design the final tools in HASTEN is summarised in the flow diagram (Figure 1). We used a modified Delphi system to analyse and confirm the final consensus.

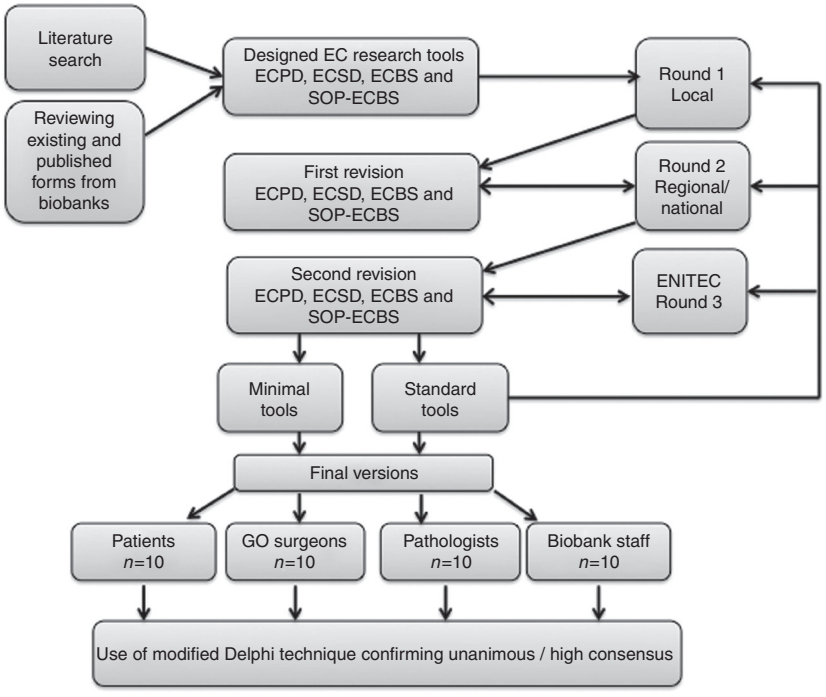

Figure 1. Flow chart illustrating our workflow in designing the EC research tools and the method of generating consensus (Endometrial cancer (EC), European Network of Individualised Treatment in Endometrial Cancer (ENITEC), Endometrial Cancer Patient Data Collection Tool (ECPD), Endometrial Cancer Surgical Data Collection Tool (ECSD), Endometrial Cancer Biospecimen Tool (ECBS), standard operating procedure for collection, processing and storage of tissue and fluid for EC research (SOP-ECBS)).

Generation of the initial tools

Literature search. We performed a systematic review of the literature using the keywords 'Endometrial Cancer', 'risk factors', 'age of presentation', 'parity', 'menopausal status', 'metformin', 'progestogens or Mirena', 'hormone replacement therapy', 'polycystic ovary syndrome', 'tamoxifen', 'bowel cancer', 'colorectal cancer', 'breast cancer', 'diabetes', 'hypertension', 'ethnicity', 'anthropometric assessment', 'smoking', 'standard operating procedure' and 'endometrium', 'blood or plasma or serum', 'saliva', 'urine', 'endometrial fluid', 'peritoneal fluid', 'biobank best practices' 'histopathology markers', 'outcomes', 'biomarkers', 'Laboratory processing procedures of tissue, blood and body fluids', 'biobanking standards', 'SOP's for collection of tissue, fluids, blood, saliva, urine' in Scopus, Discover and PubMed databases. The literature search was limited to studies published in the past 10 years. Out of 3464 papers identified in the initial search, 413 papers were selected for further detailed scrutiny based on the following inclusion criteria:

(1) Papers that investigated how the aforementioned factors affect an individual's risk of developing EC.
(2) Publications that proposed standard operating procedures (SOPs) or best practices for the collection, storage and processing of the different tissues or fluids.
(3) Papers in English language only.
(4) Papers available as full text via all available resources to the authors (e.g., online resources or library facilities at Liverpool Women's Hospital (LWH), University of Liverpool, British Medical Association or Royal College of Obstetricians and Gynaecologists.

We further conducted manual searches for the relevant manuscripts referenced in these selected papers and the relevant guidelines from the large biorepositories.

FURTHER DEVELOPMENT OF THE TOOLS

First local consultation. The local team at Liverpool, comprising of four members of surgical gynaecological oncology team, four Macmillan clinical cancer nurse specialists, two clinical academics with an interest in EC research, two pathologists, two biobank staff members and a medical student, developed the three forms (patient data collection tool, surgical data collection tool, biospecimen form) and a standard operative procedure. These forms and the SOP were based on: (a) the information gathered in the literature search; (b) by considering the forms that were already in use in LWH/University of Liverpool biobank to collect biospecimens and data in EC research studies. Liverpool Women's Hospital is a tertiary referral regional cancer centre for gynaecological cancers, and is part of the Cheshire and Merseyside strategic clinical networks, which serves a population of 2.4 million. The age-standardised incidence rate of EC in the Merseyside and Cheshire cancer network is 18.3 per 100 000 female members of the population (NCIN, 2013; Gynae Clinical Network Constitution, 2014–2015). (c) Standard operating procedures developed by the National Institutes of Health, Human Endometrial Tissue and DNA Bank for the collection, transport and storage of human endometrial tissue and blood samples of women undergoing endometrial biopsy or hysterectomy for non-malignant indications (Sheldon *et al*, 2011). (d) Sample handling and storage protocol published by the UK biobank to collect urine and blood samples (Elliott *et al*, 2008). UK biobank is a major national and international health resource, which was established by Wellcome trust, Medical Research Council, Department of Health, Scottish Government and The Northwest Regional Development Agency. The main aim of this was to improve prevention, diagnosis and treatment of many illnesses such as cancer, heart disease, stroke, diabetes, arthritis, osteoporosis and dementia.

The forms were revised and amended based on local consultation.

Second regional/national consultation. The modified versions of the three forms and the SOP mentioned above were disseminated among three regional and eight national research centres involved in EC research in the United Kingdom and forms were revised integrating their feedback and as a result, two different tools, a minimal and a standard tool were developed. This pragmatic and inclusive approach provides guidance for collecting either a minimal or the ideal 'standard' data set considering the available resources.

Third European consultation. The modified forms were then circulated to all researchers adhering to the European Network of Individualised Treatment in Endometrial Cancer (ENITEC) and were further revised according to feedback received. The revised tools were presented at the annual ENITEC face-to-face meeting in June 2016, where the minimal form was unanimously approved by all 47 attendees. Some further modifications were suggested for the standard tool, which was revised accordingly and the revised forms were repopulated to all participated in the consultations rounds 1–3 to obtain their final approval.

Consensus generation. A modified Delphi system was used to generate consensus regarding the final adapted tools. For this, the forms were disseminated to a group of selected panel members of representing all stakeholders included in all previous rounds, including patients, gynaecological oncologists, researchers, pathologists and biobank staff, randomly selected from the participants of the consultation ($n = 40$) to evaluate and score the tools using a scoring sheet recording their agreement.

Statistical analysis. The consensus was quantified using a modified Delphi technique and we have reported the median with an interquartile range and also percentages for each category of the Likert scale. A nine-point Likert scale was used, except for the patient data tool where the scale was reduced to five points to reduce complexity for patients.

RESULTS

Final tools

ECPD collection tool. A patient-friendly data collection tool (EC patient data (ECPD)) was devised to capture many important demographic variables that are directly relevant to EC research that can only be accurately recalled by the patient herself. For example, the available literature suggests that >20 kg of adult weight gain to be independently associated with increased risk of EC (Friedenreich *et al*, 2007) and this information is unlikely to be obtained easily other than directly from the patient. Many other risk factors for EC such as the age of presentation, the postmenopausal status, polycystic ovarian disease (Fearnley *et al*, 2010), nulliparity (Schonfeld *et al*, 2013), early age of menarche (Gong *et al*, 2015), family history of hereditary lynch syndrome-related cancers (Boilesen *et al*, 2008), past history of lynch syndrome-related cancers, medical conditions such diabetes (Friberg *et al*, 2007), previous use of tamoxifen (Bergman *et al*, 2000), hormone replacement therapy use (Beral *et al*, 2005) and exercise habits have been included in the tool. Some other factors with inconclusive links to EC at present such as smoking (Lindemann *et al*, 2008) were also included in anticipation of their confirmation in appropriate future studies. Table 1 and Figure 2 illustrate the outcome of the final round of consensus.

Table 1. Outcome of the final round of consensus for ECPD Tool using 5-point Likert scale

		Percentages of responses (%)				
Statements in the score sheet for patients	Score, median (IQR)	Strongly agree	Agree	Undecided	Disagree	Strongly disagree
The information asked in personal history is easy to fill	1 (1–2)	60	40	0	0	0
The questions in medical history section are easy to understand and fill	1 (1–2)	60	40	0	0	0
The questions in past history are easy to understand and fill	1 (1–2)	60	40	0	0	0
The questions in social history section are easy to understand and fill	1 (1–2)	60	30	10	0	0
Overall, the form is easy to understand and does not take much time to fill it	1.5 (1–2)	50	50	0	0	0

Abbreviations: ECPD = Endometrial Cancer Patient Data; IQR = interquartile range. IQR, five-point Likert scale: Strongly agree, Agree, Undecided, Disagree and Strongly disagree; $n = 10$.

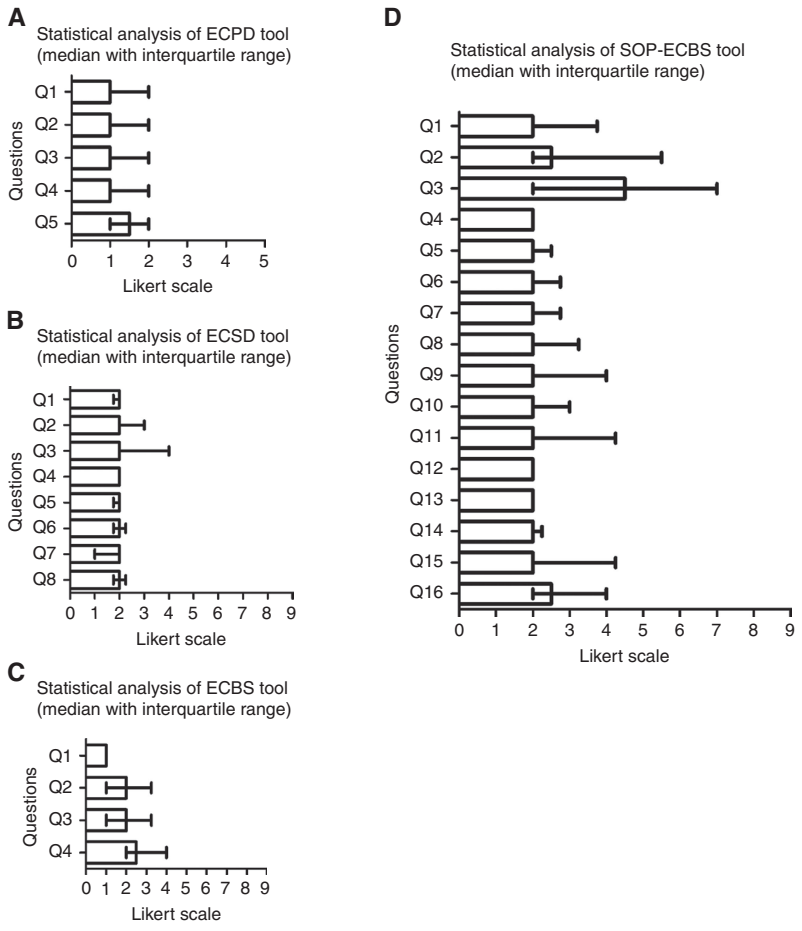

Figure 2. Statistical analysis of Endometrial Cancer Patient Data Collection Tool (ECPD), Endometrial Cancer Surgical Data Collection Tool (ECSD), Endometrial Cancer Biospecimen Tool (ECBS) and standard operating procedure for collection, processing and storage of tissue and fluid for EC research (SOP-ECBS) tools.

Score for each question in ECPD was obtained using the Likert scale, which assesses the acceptability and usability ($n = 10$). Among the panel members, only 2% were undecided on the clarity of the questions in social history section, and overall, 98% patients agreed that the tool was easy to use (Supplementary Figure S1).

ECSD collection tool. The EC surgical data (ECSD) tool included salient demographic, histological and pre/postoperative features. Demographic features such as body mass index (BMI) were included. Body mass index instead of waist-to-hip ratio or waist circumference was chosen because of its universal use and reproducibility. Although all anthropometric assessments (BMI, waist-to-hip ratio, waist and hip circumferences) are found to be strongly associated with increased risk of EC (Friedenreich *et al*, 2007), accurate data on waist-to-hip ratio or waist circumferences require additional effort using the same reference points by healthcare team and thus accurate data collection is unlikely to be universally feasible. In a recent study (Painter *et al*, 2016), BMI was

found to be a causal factor and was associated with EC compared with waist-to-hip ratio. The preoperative imaging details are helpful to assess the spread locally and to rule out distant metastases. Discordance between endometrial biopsy and final histology results has been shown to be associated with poorer survival outcome (Werner *et al*, 2013); hence, preoperative biopsy results are important. Staging details including operative findings and final histopathologic details after surgery are important when correlating with outcomes. Immunohistochemical biomarkers can be used to distinguish ECs from ovarian or cervical or other malignancies, but importantly also as prognostic biomarkers that are associated with clinical outcome (Li *et al*, 2013; Kamal *et al*, 2016). Information when collected in a standard way together with biosamples will naturally increase the internal and external validity of the generated data. The patient data collection, including follow-up and accurate documentation of cause of demise, should be updated regularly until the completion of standard follow-up period (either 3 years (minimum) or 5 years, depending on local practice). The form is arranged into three sections:

(1) Surgical data: Completed at the time of sample collection.
(2) Histopathology details: Completed after final staging and treatment.
(3) Outcome data: Documented during follow-up and finally at the end of follow-up

The results of final consensus are as shown in Table 2 and Figure 2, wherein we have calculated the median with an interquartile range. There was a high level of agreement among the panellists for all sections, except that a number of the respondents considered sections on the history, antecedent biopsy details and sample collection details to be not relevant. Overall, 96.25% of panel members agreed on different aspects of the tool (Supplementary Figure S1).

EC Biospecimen tool. Variations in the collection methods and biobanking conditions (processing and storage) may alter the molecular composition, expression and stability of biomarker profile (Zander *et al*, 2014); thus, consistency and strict adherence to standard operating procedures is vital (Moore *et al*, 2011). Therefore, biobank staff with applied experience and knowledge on clinical biobanking participated in designing, revising and obtaining final consensus on the biospecimen form. Only few respondents felt that the tissue processing (both uterine and extrauterine) section of the form was difficult to understand, while all respondents agreed on the relevance and clarity of all other sections. Overall, there was a 94% level of agreement on the different aspects of this tool. The detailed results were as shown in Table 3, Figure 2 and Supplementary Figure S1.

Standard operating procedure for collection, processing and storage of tissue and fluid for EC research. Different tissue types (both uterine and extrauterine) and body fluid types are studied in EC research. The routine investigations of these biospecimens may involve extraction of protein, RNA and DNA to be evaluated using a variety of techniques such as proteomics, genomics and metabolomics. The final SOP was designed amalgamating a number of available separate, detailed methodological protocols (e.g., for centrifugation, filtration, addition of preservatives, as well as storage temperatures). Availability of such information from a biobank will allow the scientists to accurately interpret their data, for example, to examine the metabolic profile of samples such as blood, tissue, endometrial fluid or aspirate and detect disease-specific changes with confidence, especially in multicentre studies (Assfalg *et al*, 2008; Bernini *et al*, 2009). Studies examining hormones are of major relevance to the endometrium, and in addition to more traditional samples such as blood, some have studied noninvasive specimens including saliva and urine (Shirtcliff *et al*, 2001). Noninvasive tests are of a particular interest in clinical research and future work is expected to focus more on them.

The outcome details of the final round of consensus regarding the standard operating procedure for collection, processing and storage of tissue and fluid for EC research (SOP-ECBS) are as presented in Table 4 and Figure 2. There was a general agreement

Table 2. Outcome of the final round of consensus for ECSD Tool using nine-point Likert scale

		Percentages of responses (%)								
Questions in the score sheet for gynaeoncologists	Score, median (IQR)	Strongly agree	Agree	Moderately agree	Mildly agree	Undecided	Mildly disagree	Moderately disagree	Disagree	Strongly disagree
Is the general information about patient relevant?	2 (1.75–2)	20	80	0	0	0	0	0	0	0
Is the section on history relevant?	2 (2–3)	10	60	20	0	0	0	0	10	0
Are the Imaging details relevant and sufficient?	2 (2–4)	10	80	0	30	0	0	0	0	0
Are Antecedent biopsy details relevant?	2 (2–2)	10	80	0	0	0	0	0	0	10
Is the Operative findings section relevant?	2 (1.75–2)	20	80	0	0	0	0	0	0	0
Is the Histopathology type details section relevant and sufficient?	2 (1.75–2.25)	20	60	10	10	0	0	0	0	0
Is the Sample collection details section easy to complete?	2 (1–2)	40	50	0	0	0	0	0	0	10
Are Outcome details relevant?	2 (1.75–2.25)	20	60	10	10	0	0	0	0	0

Abbreviations: ECSD = Endometrial Cancer Surgical Data; IQR = interquartile range. IQR, nine-point Likert scale: Strongly agree, Agree, Moderately agree, Mildly agree, Undecided, Mildly disagree, Disagree and Strongly disagree; $n = 10$.

Table 3. Outcome of the final round of consensus for ECBS Tool using nine-point Likert scale

		Percentages of responses (%)								
Questions in the score sheet for biobank staff	Score Median (IQR)	Strongly agree	Agree	Moderately agree	Mildly agree	Undecided	Mildly disagree	Moderately disagree	Disagree	Strongly disagree
Sample ID–Is this relevant?	1 (1–1)	90	10	0	0	0	0	0	0	0
Methods of tissue processing (Endometrium)–Is this section easy to understand?	2 (1–3.25)	40	30	10	10	0	0	0	10	0
Methods of tissue processing (Extra uterine tissue)–Is this section easy to understand?	2 (1–3.25)	40	30	10	10	0	0	0	10	0
Methods of fluid processing (Endometrial/Peritoneal/Blood/Saliva/Urine)–Is this section easy to understand?	2.5 (2–4)	10	40	10	40	0	0	0	0	0

Abbreviations: ECBS = Endometrial Cancer Biospecimen; IQR = interquartile range. IQR, nine-point Likert scale: Strongly agree, Agree, Moderately agree, Mildly agree, Undecided, Mildly disagree, Disagree and Strongly disagree; $n = 10$

on the user-friendliness and relevance of the tool. Few panellists responded that tissue and blood collection details could be modified further for clarity. Overall, 83.75% of panellists agreed, 8.75% were undecided and 7.5% disagreed with different sections of this tool.

DISCUSSION

We have developed evidence-based standard data collection forms ECPD, ECSD (minimal), ECSD (Standard) and an SOP-ECBS with inclusive participation and approval of all stakeholders in EC cancer biobanking. The final tools were approved by a large multidisciplinary team of reviewers and after reaching consensus (see Supplementary Figure S1), they are published as Supplementary Information with this open access manuscript. They will therefore be freely available to all EC researchers internationally. These tools provide a means by which to reduce confounding factors in the collected data and facilitate larger multicentre studies.

Our choice of the exact information to collect was based on critical appraisal of the best available evidence. Where no published evidence was available, consultation of the experts' opinion and the SOPs of the larger biobanks were considered. The centrifugation speed in processing blood was one such example.

We have used a modified Delphi technique, with multiple alterations from the standard technique, including multiple rounds of feedback, which allows the same panel members to reassess or reconsider initial judgment, participant anonymity, controlled feedback and statistical analysis to interpret data between the rounds. Similar variations to original Delphi system, for example, restricting the ability of the experts to respond to the original question and alterations in the expert groups, as well as changing the end point, have been used previously (Thompson, 2009).

Repeated use of a homogenous panel was unjustifiable for our research aims for the following reasons. Our endeavour was to generate separate forms for diverse end points, for example, patient data collection, surgical data collection, tissue processing information and the standard operative procedures. These obviously required panel members of diverse backgrounds, with different fields of expertise and therefore our panellists were not a homogenous group.

The main deviation from the classic technique was the number of consultation rounds and the end point. Our first two rounds were descriptive to generate opinions and ideas from different expert panels. We included their feedback to generate the finalised forms and SOP. In the final round of the consensus, we distributed a score sheet to each of the panellists along with the forms to evaluate their agreement with the final tools. Our final panel included stakeholders representing those involved in all previous panels. The high percentage of agreement observed with the statistical analysis of data obtained from the third and final round precluded the need for any further consensus rounds.

As more detailed, standardised surgical data collection will allow a comprehensive assessment of the relationship between the surgical phenotypical data with the outcomes of treatments, we strongly advise the use of the standard rather than the minimal ECSD tool. However, if the collection or quality of the large set of data or specimens cannot be guaranteed, the minimal set should be employed. We plan to regularly update these tools in the future through information obtained by feedback and review of future literature, initially on a yearly basis and 5 yearly thereafter. Future considerations in the context of our initiatives include creating an internationally funded web-based central database system allowing voluntary deposition of the information on all biospecimens collected by EC researchers worldwide, which will be easily accessible to all. This approach, we believe, will reduce costs and time spent by individual units while increasing the credibility of the data generated and will offer a transparent, common platform for newer collaborations.

'Molecular Pathological Epidemiology' (MPE) integrates pathology and epidemiology to understand the interrelationships between exogenous and endogenous factors that affect carcinogenesis, progression and response to treatment. It is a constantly evolving field in cancer research (Ogino and Stampfer, 2010). Statistical methods have also been developed to consider both molecular pathology and epidemiology to ensure novel discoveries with high clinical impact. However, the generation of such high-impact MPE studies are impeded by similar challenges including

Table 4. Outcome of the final round of consensus for SOP-ECBS Tool using nine-point Likert scale

		Percentages of responses (%)								
Questions in the score sheet for pathologists	Score Median (IQR)	Strongly agree	Agree	Moderately agree	Mildly agree	Undecided	Mildly disagree	Moderately disagree	Disagree	Strongly disagree
Is section: Processing and storage materials, relevant and easy to understand?	2 (2–3.75)	10	50	20	0	0	20	0	0	0
Is section: Collection–Tissue, relevant and easy to understand?	2.5 (2–5.5)	10	40	10	10	10	0	20	0	0
Is section: Collection–Blood, relevant and easy to understand?	4.5 (2–7)	10	30	0	10	10	10	30	0	0
Is section: Collection – Urine, relevant and easy to understand?	2 (2–2)	10	80	10	0	0	0	0	0	0
Is section: Collection – Saliva, relevant and easy to understand?	2 (2–2.5)	10	70	0	10	10	0	0	0	0
Is section: Collection – Peritoneal fluid, relevant and easy to understand?	2 (2–2.75)	0	80	0	0	20	0	0	0	0
Is section: Collection – Endometrial fluid/uterine aspirates, relevant and easy to understand?	2 (2–2.75)	0	80	0	0	20	0	0	0	0
Is section: Sample processing – Tissue, relevant and easy to understand?	2 (2–3.25)	0	70	10	10	10	0	0	0	0
Is section: Sample processing – Blood, relevant and easy to understand?	2 (2–4)	0	60	10	20	10	0	0	0	0
Is section: Sample processing – Urine, relevant and easy to understand?	2 (2–3)	0	70	20	0	0	10	0	0	0
Is section: Sample processing – Saliva, relevant and easy to understand?	2 (2–4.25)	0	60	10	10	10	10	0	0	0
Is section: Sample processing – Peritoneal fluid, relevant and easy to understand?	2 (2–2)	10	80	0	0	10	0	0	0	0
Is section: Sample processing – Endometrial fluid/uterine aspirates, relevant and easy to understand?	2 (2–2)	10	80	0	0	10	0	0	0	0
Is section: Storage and data recording, relevant and easy to understand?	2 (2–2.25)	10	70	10	0	0	10	0	0	0
Is section: Freezer check, relevant and easy to understand?	2 (2–4.25)	0	60	10	10	10	10	0	0	0
Is section: Checklist, relevant and easy to understand?	2.5 (2–4)	0	50	10	30	10	0	0	0	0

Abbreviations: IQR = interquartile range; SOP-ECBS = standard operating procedure for collection, processing and storage of tissue and fluid for EC research. IQR, nine-point Likert scale: Strongly agree, Agree, Moderately agree, Mildly agree, Undecided, Mildly disagree, Disagree and Strongly disagree; $n = 10$.

selection and recall bias, measurement errors and misclassification comparable to the traditional molecular biological studies (Hughes *et al*, 2012; Campbell *et al*, 2017). Variability in tissue retrieval rate and sample sizes leads to random and non-random selection bias, resulting in large variation of an effect estimate with wide confidence intervals and publication bias (Ogino *et al*, 2011, 2016). The use of our tools by EC biobanks will provide means with which to streamline the collection of a large amount of standardised quality assured material from well-phenotyped patients. This will in turn facilitate adequately powered studies, giving high clinical impact while also facilitating high-quality research that is attainable within an acceptable timescale.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Assfalg M, Bertini I, Colangiuli D, Luchinat C, Schäfer H, Schütz B, Spraul M (2008) Evidence of different metabolic phenotypes in humans. *Proc Natl Acad Sci USA* **105**(5): 1420–1424.

Beral V, Bull D, Reeves G, Collaborators MWS (2005) Endometrial cancer and hormone-replacement therapy in the Million Women Study. *Lancet* **365**(9470): 1543–1551.

Bergman L, Beelen ML, Gallee MP, Hollema H, Benraadt J, van Leeuwen FE (2000) Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of Liver and Endometrial cancer Risk following Tamoxifen. *Lancet* **356**(9233): 881–887.

Bernini P, Bertini I, Luchinat C, Nepi S, Saccenti E, Schäfer H, Schütz B, Spraul M, Tenori L (2009) Individual human phenotypes in metabolic space and time. *J Proteome Res* **8**(9): 4264–4271.

Boilesen AE, Bisgaard ML, Bernstein I (2008) Risk of gynecologic cancers in Danish hereditary non-polyposis colorectal cancer families. *Acta Obstet Gynecol Scand* **87**(11): 1129–1135.

Campbell PT, Rebbeck TR, Nishihara R, Beck AH, Begg CB, Bogdanov AA, Cao Y, Coleman HG, Freeman GJ, Heng YJ, Huttenhower C, Irizarry RA, Kip NS, Michor F, Nevo D, Peters U, Phipps AI, Poole EM, Qian ZR, Quackenbush J, Robins H, Rogan PK, Slattery ML, Smith-Warner SA, Song M, VanderWeele TJ, Xia D, Zabor EC, Zhang X, Wang M, Ogino S (2017) Proceedings of the third international molecular pathological epidemiology (MPE) meeting. *Cancer Causes Control* **28**(2): 167–176.

CRUK. *Uterine Cancer Statistics,* Vol. 2015. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/uterine-cancer.

Elliott P, Peakman TC, Biobank U (2008) The UK Biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine. *Int J Epidemiol* **37**(2): 234–244.

Fassbender A, Rahmioglu N, Vitonis AF, Vigano P, Giudice LC, D'Hooghe TM, Hummelshoj L, Adamson GD, Becker CM, Missmer SA, Zondervan KT, Group WEW (2014) World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project: IV. Tissue collection, processing, and storage in endometriosis research. *Fertil Steril* **102**(5): 1244–1253.

Fearnley EJ, Marquart L, Spurdle AB, Weinstein P, Webb PM, Australian Ovarian Cancer Study Group and Australian National Endometrial Cancer Study Group (2010) Polycystic ovary syndrome increases the risk of endometrial cancer in women aged less than 50 years: an Australian case–control study. *Cancer Causes Control* **21**(12): 2303–2308.

Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* **136**(5): E359–E386.

Friberg E, Orsini N, Mantzoros CS, Wolk A (2007) Diabetes mellitus and risk of endometrial cancer: a meta-analysis. *Diabetologia* **50**(7): 1365–1374.

Friedenreich C, Cust A, Lahmann PH, Steindorf K, Boutron-Ruault MC, Clavel-Chapelon F, Mesrine S, Linseisen J, Rohrmann S, Boeing H, Pischon T, Tjønneland A, Halkjaer J, Overvad K, Mendez M, Redondo ML, Garcia CM, Larrañaga N, Tormo MJ, Gurrea AB, Bingham S, Khaw KT, Allen N, Key T, Trichopoulou A, Vasilopoulou E, Trichopoulos D, Pala V, Palli D, Tumino R, Mattiello A, Vineis P, Bueno-de-Mesquita HB, Peeters PH, Berglund G, Manjer J, Lundin E, Lukanova A, Slimani N, Jenab M, Kaaks R, Riboli E (2007) Anthropometric factors and risk of endometrial cancer: the European prospective investigation into cancer and nutrition. *Cancer Causes Control* **18**(4): 399–413.

Gong TT, Wang YL, Ma XX (2015) Age at menarche and endometrial cancer risk: a dose-response meta-analysis of prospective studies. *Sci Rep* **5**: 14051.

Gynae Clinical Network Constitution (2014–2015) Available at: http://www.nwcscnsenate.nhs.uk/files/2314/1172/3867/Gynae_CNG_Constitution_2014.pdf.

Heravi-Moussavi A, Anglesio MS, Cheng SW, Senz J, Yang W, Prentice L, Fejes AP, Chow C, Tone A, Kalloger SE, Hamel N, Roth A, Ha G, Wan AN, Maines-Bandiera S, Salamanca C, Pasini B, Clarke BA, Lee AF, Lee CH, Zhao C, Young RH, Aparicio SA, Sorensen PH, Woo MM, Boyd N, Jones SJ, Hirst M, Marra MA, Gilks B, Shah SP, Foulkes WD, Morin GB, Huntsman DG (2012) Recurrent somatic DICER1 mutations in nonepithelial ovarian cancers. *N Engl J Med* **366**(3): 234–242.

Hughes LA, Williamson EJ, van Engeland M, Jenkins MA, Giles GG, Hopper JL, Southey MC, Young JP, Buchanan DD, Walsh MD, van den Brandt PA, Alexandra Goldbohm R, Weijenberg MP, English DR (2012) Body size and risk for colorectal cancers showing BRAF mutations or microsatellite instability: a pooled analysis. *Int J Epidemiol* **41**(4): 1060–1072.

International Society for Biological and Environmental Repositories (2008) *Best Practices for Respositories: Collection, Storage, Retrieval and Distribution of Biological Materials for Research*. In Cell preservation technology, Vol 6, 2nd edition. Mary Ann Liebert, Inc.: New Rochelle, NY, USA.

Kamal A, Tempest N, Parkes C, Alnafakh R, Makrydima S, Adishesh M, Hapangama DK (2016) Hormones and endometrial carcinogenesis. *Horm Mol Biol Clin Invest* **25**(2): 129–148.

Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, Robertson AG, Pashtan I, Shen R, Benz CC, Yau C, Laird PW, Ding L, Zhang W, Mills GB, Kucherlapati R, Mardis ER, Levine DA, Network CGAR (2013) Integrated genomic characterization of endometrial carcinoma. *Nature* **497**(7447): 67–73.

Li MZL, Qi W, Shen D, Li X, Wang J, Wei L (2013) Clinical implications and prognostic value of five biomarkers in endometrial carcinoma. *Chin-German J Clinl Oncol* **12**(12): 586–591.

Lindemann K, Eskild A, Vatten LJ, Bray F (2010) Endometrial cancer incidence trends in Norway during 1953–2007 and predictions for 2008–2027. *Int J Cancer* **127**(11): 2661–2668.

Lindemann K, Vatten LJ, Ellstrøm-Engh M, Eskild A (2008) Body mass, diabetes and smoking, and endometrial cancer risk: a follow-up study. *Br J Cancer* **98**(9): 1582–1585.

Moore HM, Kelly A, Jewell SD, McShane LM, Clark DP, Greenspan R, Hainaut P, Hayes DF, Kim P, Mansfield E, Potapova O, Riegman P, Rubinstein Y, Seijo E, Somiari S, Watson P, Weier HU, Zhu C, Vaught J (2011) Biospecimen reporting for improved study quality. *Biopreserv Biobank* **9**(1): 57–70.

Morente MM, de Alava E, Fernandez PL (2007) Tumour banking: the Spanish design. *Pathobiology* **74**(4): 245–250.

National Cancer Institute (2011) Best Practices For Biospecimen Resources. NIH: Bethesda, MD, USA. Available at: https://biospecimens.cancer.gov/practices/2011bp.asp.

National Cancer Institute (2016) Best Practices For Biospecimen Resources. NIH: Bethesda, MD, USA. Available at: https://biospecimens.cancer.gov/bestpractices/2016-NCIBestPractices.pdf.

NCIN (2013) *Outline of Uterine Cancer in the United Kingdom: Incidence, Mortality and Survival*. NCIN. PHE Knowledge and Intelligence Team (East Midlands): Sheffield, UK.

Ogino S, Chan AT, Fuchs CS, Giovannucci E (2011) Molecular pathological epidemiology of colorectal neoplasia: an emerging transdisciplinary and interdisciplinary field. *Gut* **60**(3): 397–411.

Ogino S, Nishihara R, VanderWeele TJ, Wang M, Nishi A, Lochhead P, Qian ZR, Zhang X, Wu K, Nan H, Yoshida K, Milner Jr DA, Chan AT, Field AE, Camargo Jr CA, Williams MA, Giovannucci EL (2016) Review article: the role of molecular pathological epidemiology in the study of neoplastic and non-neoplastic diseases in the era of precision medicine. *Epidemiology* **27**(4): 602–611.

Ogino S, Stampfer M (2010) Lifestyle factors and microsatellite instability in colorectal cancer: the evolving field of molecular pathological epidemiology. *J Natl Cancer Inst* **102**(6): 365–367.

Painter JN, O'Mara TA, Marquart L, Webb PM, Attia J, Medland SE, Cheng T, Dennis J, Holliday EG, McEvoy M, Scott RJ, Ahmed S, Healey CS, Shah M, Gorman M, Martin L, Hodgson SV, Beckmann MW, Ekici AB, Fasching PA, Hein A, Rübner M, Czene K, Darabi H, Hall P, Li J, Dörk T, Dürst M, Hillemanns P, Runnebaum IB, Amant F, Annibali D, Depreeuw J, Lambrechts D, Neven P, Cunningham JM, Dowdy SC, Goode EL, Fridley BL, Winham SJ, Njølstad TS, Salvesen HB, Trovik J, Werner HM, Ashton KA, Otton G, Proietto A, Mints M, Tham E, Bolla MK, Michailidou K, Wang Q, Tyrer JP, Hopper JL, Peto J, Swerdlow AJ, Burwinkel B, Brenner H, Meindl A, Brauch H, Lindblom A, Chang-Claude J, Couch FJ, Giles GG, Kristensen VN, Cox A, Pharoah PD, Tomlinson I, Dunning AM, Easton DF, Thompson DJ, Spurdle AB, Group A, RENDOCAS f, (NSECG) NSoECGG, (ANECS) ANECSG (2016) Genetic risk score Mendelian randomization shows that obesity measured as body mass index, but not waist:hip ratio, is causal for endometrial cancer. *Cancer Epidemiol Biomarkers Prev* **25**(11): 1503–1510.

Rahmioglu N, Fassbender A, Vitonis AF, Tworoger SS, Hummelshoj L, D'Hooghe TM, Adamson GD, Giudice LC, Becker CM, Zondervan KT, Missmer SA, Group WEW (2014) World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project: III. Fluid biospecimen collection, processing, and storage in endometriosis research. *Fertil Steril* **102**(5): 1233–1243.

Ransohoff DF, Gourlay ML (2010) Sources of bias in specimens for research about molecular markers for cancer. *J Clin Oncol* **28**(4): 698–704.

Schonfeld SJ, Hartge P, Pfeiffer RM, Freedman DM, Greenlee RT, Linet MS, Park Y, Schairer C, Visvanathan K, Lacey JV (2013) An aggregated analysis of hormonal factors and endometrial cancer risk by parity. *Cancer* **119**(7): 1393–1401.

Sheldon E, Vo KC, McIntire RA, Aghajanova L, Zelenko Z, Irwin JC, Giudice LC (2011) Biobanking human endometrial tissue and blood specimens: standard operating procedure and importance to reproductive biology research and diagnostic development. *Fertil Steril* **95**(6): 2120–2122.e1–e12.

Shirtcliff EA, Granger DA, Schwartz E, Curran MJ (2001) Use of salivary biomarkers in biobehavioral research: cotton-based sample collection methods can interfere with salivary immunoassay results. *Psychoneuroendocrinology* **26**(2): 165–173.

Thompson M (2009) Considering the implication of variations within Delphi research. *Fam Pract* **26**(5): 420–424.

Tworoger SS, Hankinson SE (2006) Use of biomarkers in epidemiologic studies: minimizing the influence of measurement error in the study design and analysis. *Cancer Causes Control* **17**(7): 889–899.

Vaught J, Lockhart NC (2012) The evolution of biobanking best practices. *Clin Chim Acta* **413**(19-20): 1569–1575.

Vitonis AF, Vincent K, Rahmioglu N, Fassbender A, Buck Louis GM, Hummelshoj L, Giudice LC, Stratton P, Adamson GD, Becker CM, Zondervan KT, Missmer SA, Group WEW (2014) World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project: II. Clinical and covariate phenotype data collection in endometriosis research. *Fertil Steril* **102**(5): 1223–1232.

Werner HMJ, Trovik J, Marcickiewicz J, Tingulstad S, Staff AC, Engh ME, Oddenes K, Rokne JA, Tjugum J, Lode MS, Amant F, Salvesen HB (2013) A discordant histological risk classification in preoperative and operative biopsy in endometrial cancer is reflected in metastatic risk and prognosis. *Eur J Cancer* **49**: 625–632.

Wiegand KC, Shah SP, Al-Agha OM, Zhao Y, Tse K, Zeng T, Senz J, McConechy MK, Anglesio MS, Kalloger SE, Yang W, Heravi-Moussavi A, Giuliany R, Chow C, Fee J, Zayed A, Prentice L, Melnyk N, Turashvili G, Delaney AD, Madore J, Yip S, McPherson AW, Ha G, Bell L, Fereday S, Tam A, Galletta L, Tonin PN, Provencher D, Miller D, Jones SJ, Moore RA, Morin GB, Oloumi A, Boyd N, Aparicio SA, Shih IeM, Mes-Masson AM, Bowtell DD, Hirst M, Gilks B, Marra MA, Huntsman DG (2010) ARID1A mutations in endometriosis-associated ovarian carcinomas. *N Engl J Med* **363**(16): 1532–1543.

Yuille M, van Ommen GJ, Bréchot C, Cambon-Thomsen A, Dagher G, Landegren U, Litton JE, Pasterk M, Peltonen L, Taussig M, Wichmann HE, Zatloukal K (2008) Biobanking for Europe. *Brief Bioinform* **9**(1): 14–24.

Zander J, Bruegel M, Kleinhempel A, Becker S, Petros S, Kortz L, Dorow J, Kratzsch J, Baber R, Ceglarek U, Thiery J, Teupser D (2014) Effect of biobanking conditions on short-term stability of biomarkers in human serum and plasma. *Clin Chem Lab Med* **52**(5): 629–639.

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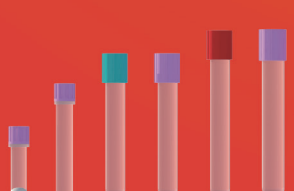

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广州阳普医疗科技股份有限公司
GuangZhou Improve Medical Instruments Co.,LTD.

广州市经济技术开发区科学城开源大道102号
No.102 Kaiyuan Avenue,Science City,Guangzhou Economic&Technological Development District,Guangzhou,China
Tel: +86 20-3231-2678
Fax:+86 20-3201-6465
Website: www.improve-medical.com
PC:510530