同源重组缺陷分析（SigMA算法）\*

\*仅供科研使用

多变量突变签名分析（Signature Multivariate Analysis ,SigMA）是一种新的计算工具，可用于准确检测靶基因组中与同源重组修复（homologous recombination repair, HR）功能缺陷相关的突变特征。研究表明，采用该算法鉴定为HR缺陷的细胞系显示出对多聚二磷酸腺苷核糖聚合酶抑制剂（poly ADP-ribose polymerase inhibitor, PARPi)的显著反应，且采用该算法鉴定为HR缺陷的卵巢癌患者表现出明显更长的铂存活率。

突变签名分析是一种强大的计算体细胞突变产生过程的算法。由于不同的过程会产生不同的突变类型（例如紫外线辐射常导致CC或CT序列的C-to-T改变），所以从概念上讲，这种分析是基于观察特异性的碱基变化以判断出不同的突变产生过程。目前，WES和WGS的数千个肿瘤样本测序结果已鉴定了癌症中的近40种突变签名，其中一些签名已确定与特定的突变过程相匹配，包括内源性的（例如复制时钟，DNA修复机制缺陷）和外源性的（例如吸烟，紫外线辐射）。

在乳腺癌中，一项具有里程碑意义的560人全基因组研究及后续研究发现，这些突变签名中的一种‘Signature 3’ (Sig3)，对应HR缺陷。可以在如下肿瘤中观察到这种突变签名：BRCA1/2完全失活-无论体细胞突变或胚系突变，BRCA1基因高甲基化，或PALB2/RAD51D基因的功能缺失性突变。在体外实验中，BRCA−/−细胞系中可观察到Sig3，这是其关联的直接证据。

重要的是，越来越多的证据表明，Sig3不仅局限于BRCA1/2或其他HR相关基因胚系突变，这在临床中有重要意义，因为那些在已知HR基因中无缺陷但是表现出Sig3的患者可能受益于PARPi治疗。最近一项乳腺癌类的研究已表明，高Sig3突变与PARPi响应更好相关。

以往对突变签名分析是基于全外显子组或全基因组测序数据的，但WES/WGS在临床使用存在着较大的局限性。SigMA通过采用基于似然度拟合与机器学习相结合，成功实现在Panel测序中鉴定包括Sig3在内的突变签名，是临床基因测序分析的一项重大突破。其对临床的重要意义在于，应用这种方法将有可能大幅增加受益于HR缺陷肿瘤的治疗方案的患者数量。

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| {{ pict.detectdetail\_sigma\_a }} |

a 730个乳腺癌WGS数据根据其签名分数组成簇（cluster）；簇分为四类（Sig3，APOBEC，Clock，MSI）

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| {{ pict.detectdetail\_sigma\_b }} |

图 b 四种其他肿瘤类型的簇分类：卵巢腺癌，骨肉瘤，前列腺腺癌，胰腺癌。

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| {{ pict.detectdetail\_sigma\_c }} |

图 c 与独立使用Cosine算法和NNLS算法相比，SigMA的灵敏度曲线，从左至右依次为400+ Gene Panel、WES、WGS。

经内部数据的计算机模拟计算，鼎晶OncoDrug-Seq泛癌种580 Gene Panel在性能上有进一步提升。

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| {{ pict.detectdetail\_sigma\_d }} |

图 d 同一样本WGS与Panel模拟的突变谱示例。

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| {{ pict.detectdetail\_sigma\_e }} |

图 e 在多种肿瘤细胞系研究中，四种PARP抑制剂在SigMA评价为Sig3-和Sig3+细胞中的pIC50值的综合结果（n = 366,371,369和340）。

Abbreviation Explanation -FPR: False positive rate假阳性率；Cosine余弦相似性，一种相似度算法；NNLS：Non-negative Least Squares非负最小二乘法，一种经典签名分析算法。WGS: Whole Genome Sequencing全基因组测序。pIC50达到50%抑制效果时抑制剂的浓度值的10的负对数。

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