RediScore

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Name: Report No:

SAMPLE INFORMATION

Name:	**Date Sp. Extracted:** -
Medical ID:	**Req. Physician:**
Date Of Birth:	**Report No:**
Material #1:	**Date Received:**
Material #2:	**Date Of Report:**
Sample #1 ID:	**Tumor type:**

RediScore: Homologous Recombination Deficiency (HRD) analysis

Report Summary

The computation of HRD status is based on the combined test of the GIS score and the mutation analysis of *BRCA1/2* genes in the cancer tissue.

HRD status	GIS[1] score	*BRCA1/2* status in tumor tissue
HRD positive	**High**	**Negative**

[1] GIS: Genomic Instability Score (LOH+LST+TAI)

Results and Interpretation*

Biomarker	Result	Approved therapies for indication	Therapies with potential benefit	Therapies with potential resistance/toxicity	Clinical Trials
Genomic Instability Score (GIS)	49 (High)	Olaparib (1A.1)	Rucaparib (2C.1) Talazoparib (2C.1) Niraparib (2C.1)	-	yes
BRCA1	No known pathogenic mutation was identified in the patient's tumor tissue	-	-	-	-
BRCA2	No known pathogenic mutation was identified in the patient's tumor tissue	-	-	-	-

*Note: Variants' Level of Evidence (LoE) (e.g. 1A.1, 2C.1, 1B etc) are based on the Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. For a detailed description of the recommendation please refer to Fig. 1

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Associated Treatments Information

Olaparib

DrugBank

Olaparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular homeostasis, such as DNA transcription, cell cycle regulation, and DNA repair. Olaparib has been shown to inhibit growth of select tumor cell lines in vitro and decrease tumor growth in mouse xenograft models of human cancer both as monotherapy or following platinum-based chemotherapy. Increased cytotoxicity and anti-tumor activity following treatment with olaparib were noted in cell lines and mouse tumor models with deficiencies in BRCA. In vitro studies have shown that olaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complex, resulting in disruption of cellular homeostasis and cell death. Olaparib is available as oral tablets marketed under the brand name Lynparza.

It is indicated for the following conditions:

Ovarian cancer

- For the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy.
- In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability.
- For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.
- For the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

Breast cancer

- For the treatment of adult patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Latest research supports the use of adjuvant olaparib in patients with high-risk early-stage HER2-negative breast cancer and germline BRCA mutations (PMID: 34081848).

Pancreatic cancer

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- For the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen.

Prostate cancer

- For the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone.

Rucaparib

DrugBank

Rucaparib is a potent mammalian poly(ADP-ribose) polymerase (PARP) 1, 2 and 3 inhibitor with anticancer properties. PPAR is an enzyme that plays an essential role in DNA repair by activating response pathways and facilitating repair , and defects in these repair mechanisms have been demonstrated in various malignancies, including cancer. Regulation of repair pathways is critical in promoting necessary cell death. BRCA genes are tumor suppressor genes mediate several cellular process including DNA replication, transcription regulation, cell cycle checkpoints, apoptosis, chromatin structuring and homologous recombination (HR). Homologous recombination deficiency (HRD), along with PPAR inhibition, is a vulnerability that enhances the cell death pathway when the single mutations alone would permit viability. Ovarian cancer commonly possesses defects in DNA repair pathways such as HRD due to BRCA mutations or otherwise. There are three main types of ovarian cancer: epithelial (90%), germ cell (5%) and sex cord stromal cell (5%). Epithelial ovarian, being the most common, fifth leading cause of cancer-related deaths in women in the United States. Advanced ovarian cancer particularly poses challenges due to reduced therapeutic response rates from standard platinum-based chemotherapy and overall survival rates. Rucaparib has shown to induce cytotoxicity in tumor cell lines with deficiencies in BRCA1/2 and other DNA repair genes . Of all the BRCA1/2 mutations in ovarian cancer, most are due to germline mutations (18%), and approximately 7% represent somatic mutations acquired within the tumor . The indication of rucaparib as an oral monotherapy in patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer was granted accelerated approval in 2016 for selected patients who have previously received greater than two lines of platinum-based therapy. It is currently marketed in the US under the brand name Rubraca that contains rucaparib camsylate as the active ingredient. It is indicated for:

Ovarian cancer

- for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.
- for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies.

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Prostate cancer

- for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxane-based chemotherapy. This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Talazoparib

DrugBank

Talazoparib was approved by the FDA for use in germline BRCA mutated, HER2 negative, locally advanced or metastatic breast cancer on October 16, 2018 under the trade name Talzenna . Talzenna was granted approval based on the results of the EMBRACA trial in which talazoparib resulted in a mean 8.6 months progression-free survival time versus physician's choice chemotherapy which resulted in 5.6 months progression-free survival.

Talazoparib is indicated for the treatment of adult aptients with deleterious or suspected deleterious germline BRCA mutated, HER2 negative locally advanced or metastatic breast cancer.

Niraparib

DrugBank

Niraparib is an orally active PARP inhibitor to treat ovarian cancer. FDA approval on March 2017. It is marketed under the brand name Zejula.

Niraparib is indicated for:

- the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy
- for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy
- for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either:
    - a deleterious or suspected deleterious BRCA mutation, or
    - genomic instability and who have progressed more than six months after response to the last platinum-based chemotherapy.

Clinical Trials to consider

Homologous Recombination Deficiency (HRD) associated clinical trials

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NCT03737643	Phase 3
Title	Durvalumab Treatment in Combination With Chemotherapy and Bevacizumab, Followed by Maintenance Durvalumab, Bevacizumab and Olaparib Treatment in Advanced Ovarian Cancer Patients
Treatment	Bevacizumab|Durvalumab|Olaparib|Placebo olaparib|Durvalumab placebo|Carboplatin+Paclitaxel
Location	United States

NCT04884360	Phase 3
Title	D9319C00001- 1L OC Mono Global RCT
Treatment	Olaparib|Matching placebo
Location	Chile,China

NCT04123366	Phase 2
Title	Study of Olaparib (MK-7339) in Combination With Pembrolizumab (MK-3475) in the Treatment of Homologous Recombination Repair Mutation (HRRm) and/or Homologous Recombination Deficiency (HRD)-Positive Advanced Cancer (MK-7339-007/KEYLYNK-007)
Treatment	Olaparib|Pembrolizumab
Location	United States,Argentina

NCT04417192	Phase 2
Title	Olaparib Monotherapy and Olaparib + Pembrolizumab Combination Therapy for Ovarian Cancer
Treatment	Olaparib|Pembrolizumab
Location	Japan

NCT03742895	Phase 2
Title	Efficacy and Safety of Olaparib (MK-7339) in Participants With Previously Treated, Homologous Recombination Repair Mutation (HRRm) or Homologous Recombination Deficiency (HRD) Positive Advanced Cancer (MK-7339-002 / LYNK-002)
Treatment	Olaparib
Location	United States

NCT02401347	Phase 2

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Title	Phase II Trial of Talazoparib in BRCA1/2 Wild-type HER2-negative Breast Cancer and Other Solid Tumors
Treatment	Talazoparib Tosylate
Location	United States

NCT05126433	**Phase 2**
Title	Lurbinectedin Monotherapy in Participants With Advanced or Metastatic Solid Tumors
Treatment	Lurbinectedin
Location	United States

NCT04780945	**Phase 2**
Title	Functional Analysis of BRCAness
Treatment	Functional RAD51 assay|Olaparib Oral Product
Location	Netherlands

NCT04284852	**Phase 2**
Title	Niraparib Maintenance in Patients With Advanced Ovarian Cancer at Neoadjuvant Setting
Treatment	Niraparib
Location	Hong Kong

NCT03699449	**Phase 2**
Title	An uMbrella Study of BIomarker-driven Targeted Therapy In Patients With Platinum-resistant Recurrent OvariaN Cancer(AMBITION)
Treatment	olaparib+cediranib combination therapy|durvalumab + olaparib combination therapy|durvalumab + chemotherapy treatment|durvalumab + tremelimumab + chemotherapy treatment|durvalumab + tremelimumab + paclitaxel treatment|durvalumab +chemotherapy treatment
Location	Korea, Republic of

NCT04556071	**Phase 2**
Title	Efficacy and Safety of Niraparib Combined With Bevacizumab in Platinum Refractory/Resistant Recurrent Ovarian Cancer
Treatment	Niraparib|Bevacizumab

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Location	China

NCT05288127	**Phase 2**
Title	Efficacy of Talazoparib in Asian Metastatic Breast Cancer Patients With a Homologous Recombinant Deficiency (HRD) Signature
Treatment	Talazoparib
Location	Malaysia

NCT04240106	**Phase 2**
Title	Niraparib Plus Aromatase Inhibitors for Luminal-like(HER2-,ER+) and gBRCA or HDR+ Metastatic Breast Cancer (LUZERN)
Treatment	Niraparib 100 MG|Aromatase Inhibitors
Location	Spain

NCT04038502	**Phase 2**
Title	Carboplatin or Olaparib for BRcA Deficient Prostate Cancer
Treatment	Carboplatin|Olaparib
Location	United States

NCT03462342	**Phase 2**
Title	Combination ATR and PARP Inhibitor (CAPRI) Trial With AZD6738 and Olaparib in Recurrent Ovarian Cancer
Treatment	Olaparib Pill|AZD6738
Location	United States

NCT03442556	**Phase 2**
Title	Docetaxel, Carboplatin, and Rucaparib Camsylate in Treating Patients With Metastatic Castration Resistant Prostate Cancer With Homologous Recombination DNA Repair Deficiency
Treatment	Carboplatin|Docetaxel|Laboratory Biomarker Analysis|Rucaparib Camsylate|Rucaparib
Location	United States

NCT03297606	**Phase 2**
Title	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

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Treatment	Olaparib|Dasatinib|Nivolumab plus Ipilimumab|Axitinib|Bosutinib|Crizotinib|Palbociclib|Sunitinib|Temsirolimus|Erlotinib|Trastuzumab plus Pertuzumab|Vemurafenib plus Cobimetinib|Vismodegib
Location	Canada

NCT04174716	**Phase 1|Phase 2**
Title	Basket Trial of IDX-1197, a PARP Inhibitor, in Patients With HRR Mutated Solid Tumors (VASTUS)
Treatment	IDX-1197
Location	Korea, Republic of

NCT04826341	**Phase 1|Phase 2**
Title	A Phase I/II Study of Sacituzumab Govitecan Plus Berzosertib in Small Cell Lung Cancer and Homologous Recombination-Deficient Cancers Resistant to PARP Inhibitors
Treatment	Berzosertib|Sacituzumab Govitecan
Location	United States

NCT03574779	**Phase 1|Phase 2**
Title	A Study to Evaluate the Efficacy and Safety of Novel Treatment Combinations in Participants With Ovarian Cancer
Treatment	Niraparib|TSR-042|Bevacizumab|Carboplatin|Paclitaxel
Location	United States

NCT04518501	**Phase 1|Phase 2**
Title	Fuzuloparib Arsenic Trioxide Platinum Resistance Relapsed Ovarian Cancer
Treatment	Arsenic trioxide Tablet +Fuzuloparib Capsules
Location	China

NCT05252390	**Phase 1|Phase 2**
Title	NUV-868 as Monotherapy and in Combination With Olaparib or Enzalutamide in Adult Patients With Advanced Solid Tumors
Treatment	NUV-868|Olaparib|Enzalutamide
Location	United States

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Name: Report No:

NCT03337087	Phase 1|Phase 2
Title	Liposomal Irinotecan, Fluorouracil, Leucovorin Calcium, and Rucaparib in Treating Patients With Metastatic Pancreatic, Colorectal, Gastroesophageal, or Biliary Cancer
Treatment	Fluorouracil|Irinotecan Sucrosofate|Laboratory Biomarker Analysis|Leucovorin Calcium|Rucaparib
Location	United States

NCT03995017	Phase 1|Phase 2
Title	Rucaparib Plus Ramucirumab With or Without Nivolumab in Advanced Gastric and Esophageal Adenocarcinoma
Treatment	Rucaparib|Ramucirumab|Nivolumab
Location	United States

NCT03462212	Phase 1|Phase 2
Title	Carboplatin-Paclitaxel-Bevacizumab vs Carbo-Pacli-Beva-Rucaparib vs Carbo-Pacli-Ruca, Selected According to HRD Status, in Patients With Advanced Ovarian, Primary Peritoneal and Fallopian Tube Cancer, Preceded by a Phase I Dose Escalation Study on Ruca-Beva Combination
Treatment	Carboplatin|Paclitaxel|Bevacizumab|Rucaparib
Location	Italy

NCT04503265	Phase 1|Phase 2
Title	A Trial of AMXI-5001 for Treatment in Patients With Advanced Malignancies
Treatment	AMXI-5001:Dose Escalation Phase I|AMXI-5001:Dose Expansion Phase II
Location	United States

NCT02264678	Phase 1|Phase 2
Title	Ascending Doses of Ceralasertib in Combination With Chemotherapy and/or Novel Anti Cancer Agents
Treatment	Administration of ceralasertib in combination with carboplatin|Administration of ceralasertib|Administration of ceralasertib in combination with olaparib|Administation of ceralasertib in combination with durvalumab
Location	United States

NCT03317392	Phase 1|Phase 2
Title	Testing the Safety of Different Doses of Olaparib Given Radium-223 for Men With Advanced Prostate Cancer With Bone Metastasis

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Treatment	Laboratory Biomarker Analysis|Olaparib|Quality-of-Life Assessment|Radium Ra 223 Dichloride
Location	United States

NCT04890613	**Phase 1**
Title	Study of CX-5461 in Patients With Solid Tumours and BRCA1/2, PALB2 or Homologous Recombination Deficiency (HRD) Mutation
Treatment	CX-5461
Location	United States

NCT03209401	**Phase 1**
Title	Niraparib Plus Carboplatin in Patients With Homologous Recombination Deficient Advanced Solid Tumor Malignancies
Treatment	Niraparib|Carboplatin
Location	United States

NCT01434316	**Phase 1**
Title	Veliparib and Dinaciclib in Treating Patients With Advanced Solid Tumors
Treatment	Dinaciclib|Veliparib
Location	United States

Press here for a live search of clinical trials for Homologous Recombination Deficiency (HRD)

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Methodology

BRCA1/2 Next Generation Sequence (NGS) analysis

Mutations in the *BRCA1* and *BRCA2* genes lead to an increased risk of developing breast or ovarian cancer as part of hereditary breast-ovarian cancer syndrome. Recent studies have established that these genes can also be involved in the development of non-hereditary, sporadic tumors, since a proportion of ovarian, breast cancer and prostate cancer tumors contain somatic (tumor only) *BRCA1* and *BRCA2* pathogenic variants. Patients with tumors that harbor a somatic BRCA mutation may benefit from treatment with PARP inhibitors.

Genomic DNA was extracted from the FFPE tumor tissue. Analysis was carried out using a commercially available Oncomine assay (Thermo Fisher Scientific). Sequencing was carried out using the Next Generation Sequencing platform Ion GeneStudio™ S5 Prime System (Thermo Fisher Scientific). The presence of large genomic rearrangements is investigated computationally using the IonReporter Software 5.18 (Thermo Fisher Scientific) and verified by use of the MLPA method (Multiplex Ligation-dependent Probe Amplification, BRCA1: P002, BRCA2: P045, MRC Holland; AJHG 67:841-50, 2000)..

*Notes:

[1] Macrodissection was performed on the cancerous tissue

[2] Large genomic rearrangement analysis when performed in FFPE tissue has lower sensitivity compared to whole peripheral blood

[2] Each molecular analysis has an internal error probability of 0,5-1%. This is due to rare molecular events and factors involved in the production and analysis of specimens.

Genomic Instability Score (GIS) analysis

Genomic DNA was extracted from the FFPE tumor tissue. Subsequently, hybridization was carried out on the Oncoscan SNP array (Thermo Fisher Scientific). Chromosome Analysis Suite (ChAS) software along with bioinformatic and statistical algorithms were used to calculate Loss of Heterozygocity (LOH), number of telomeric-allelic imbalance (NTAI) and large-scale state transition (LST). The total value of genomic instability is given as a score (Genomic Instability Score, GIS) and is the sum of the three components.

A GIS score ≥42 is considered as positive. The computation of HRD status is based on the combined test of the GIS score and the mutation analysis of BRCA1/2 genes in the cancer tissue.

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Appendix

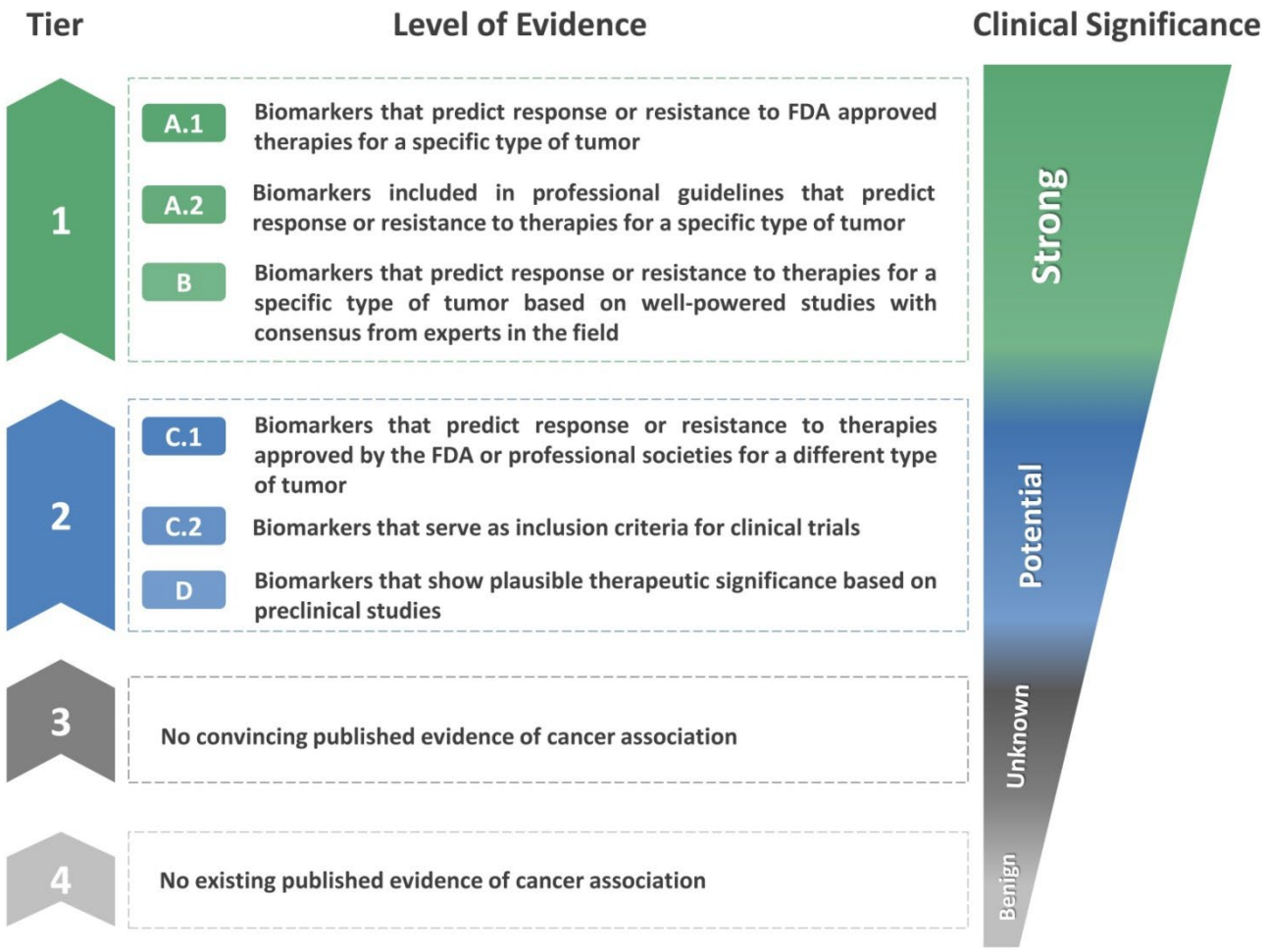

Figure 1. Joint consensus recommendation of AMP, ACMG, ASCO and CAP for reporting genetic variants in cancer. [1-2]

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