HEALTH RESEARCH IN AFRICA
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Original Article

KRAS and BRAF Mutations as Prognosis Factors in Breast Cancer

Mutations de KRAS et BRAF Comme Facteurs Pronostiques dans le Cancer du Sein

Ngo Pambe CJ[1], Rissia F[2], Mendimi Nkodo JM[3], Serrano JL[4]

Affiliations
1. Faculty of Medicine and Biomedical Sciences, The University of Garoua
2. Faculty of Health Sciences, University Marien Ngouabi of Brazzaville
3. Faculty of Medicine and Biomedical Sciences, The University of Yaounde I
4. Institute of Biomedicine and Biotechnology of Cantabria, University of Cantabria

Corresponding author:
Ngo Pambe Christiane Judith
Pathologist
Faculty of Medicine and Biomedical Sciences
The University of Garoua. Cameroun
Tél: + 237 690 80 56 68. E-mail: jupambe@yahoo.fr

Keywords: KRAS – BRAF – Mutations – Prognosis factors – Breast cancer

Mots clés: KRAS – BRAF – Mutations – Facteurs pronostiques – Cancer du sein

ABSTRACT

Introduction. Breast cancer is most often linked to genetic factors. The main signaling pathways encountered in this pathology are PIK3/AKT/mTOR and RAS/RAF/MEK/ERK. The latter is much less activated in breast cancer. KRAS and BRAF mutations are less frequent in breast cancer and their real incidence cannot be precisely determined, given the limited and sporadic studies on the subject. This work aimed to show the importance of testing for KRAS and BRAF mutation. From our search, both genes had mostly amplifications than mutations. **Methodology**. To achieve our goal, we analyzed databases from bioinformatics portals and PubMed and Google Scholar, using Medical Subject Heading terms. **Results.** The latter were somatic, accounting for 0.7% for KRAS and 0.8% for BRAF. The isoform G12 was the most frequent mutated locus for KRAS and the D594 for BRAF. These mutated D594 have opposite molecular, clinical and prognosis implications. Moreover, these mutations are most often found in triple-negative breast cancers, which are not very common in the general population, but are often found in black women. Furthermore, these mutations are often associated with a good tumor immune microenvironment and a good prognosis and overall survival. **Conclusion.** BRAF mutations with their association with tumor mutational burden make them a potential target for immune checkpoint inhibitors.

RÉSUMÉ

Introduction. Le cancer du sein est souvent lié à des facteurs génétiques. Les principales voies de signalisation rencontrées sont PIK3/AKT/mTOR et RAS/RAF/MEK/ERK. Cette dernière est beaucoup moins activée. Les mutations de KRAS et BRAF sont moins fréquentes dans le cancer du sein et leur incidence réelle ne peut être déterminée avec précision, étant donné les études limitées et sporadiques. Ce travail avait pour but de montrer l'importance du dépistage des mutations KRAS et BRAF. **Méthodologie.** Pour atteindre notre objectif, nous avons analysé des bases de données provenant de portails bioinformatiques, de PubMed et de Google Scholar, en utilisant des termes Medical Subject Heading. **Résultats.** Les deux gènes présentaient davantage d'amplifications que de mutations. Ces dernières étaient somatiques, représentant 0,7 % pour KRAS et 0,8 % pour BRAF. L'isoforme G12 était le locus muté le plus fréquent pour KRAS et le D594 pour BRAF. Ces mutations D594 ont des implications moléculaires, cliniques et pronostiques. Elles sont souvent retrouvées dans le type triple négatif, qui sont l'apanage des femmes noires. En outre, ces mutations sont souvent associées à un bon microenvironnement immunitaire de la tumeur, à un bon pronostic et une bonne survie globale. **Conclusion.** Les mutations BRAF et leur association avec la charge mutationnelle de la tumeur en font une cible potentielle pour les inhibiteurs de points de contrôle immunitaire.

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HIGHLIGHTS

What is known about the subject

- KRAS and BRAF mutations are frequently observed in other cancers.

The question addressed in this study

- We hypothesized that BRAF and KRAS mutations are correlated with prognosis in some molecular types of breast cancer and patient survival.

What this study brings new

- BRAF mutations with their association with tumor mutational burden make them a potential target for immune checkpoint inhibitors
- BRAF mutations having a better overall survival than KRAS mutations

Implications for practice, policy or future research

- Larger studies on mutations in these two genes in this subpopulation could help to understand and improve the management of this disease in this group

INTRODUCTION

It is estimated 19.3 million new cases of cancer in the world in 2020. This disease, based on genetic alterations, was responsible for approximately 10 million of deaths that year. In the 0-74 age group, the risk of developing cancer is 20%, and the risk of dying from it, 10% (1, 2). Breast cancer is the most diagnosed of all cancers in women. It is a complex disease, with a difficult-to-predict course (3). Breast cancer is most often linked to genetic factors and more particularly to a mutation in the BRCA1 and BRCA2 genes, but also PTEN, CDH1, TP53 and STK11 genes (4).

Alterations in other genes like in phosphatidyl inositol 3 -kinase (PI3K) and the mitogen activated protein kinase (MAPK) are found in signaling pathways whose discovery has allowed the development of targeted or even personalized therapies (5). These therapies act on the main signaling pathways, namely the PIK3/AKT/mTOR pathway and the RAS/RAF/MEK/ERK While the former is very frequently activated in breast cancers, the latter is much less so (6–8). In recent years, studies have found the presence of other types of mutations in breast cancer, in particular those of the BRAF and KRAS genes. Both genes are found mutated at high prevalence in other tumors as 90% and 50% in pancreatic and colon cancer for the RAS mutation; 70% and 50% in melanoma and papillary thyroid cancer respectively for the BRAF mutation (9). These genes both belong to the MAPK/ERK pathway.

KRAS is located in chromosome 12p12.1. RAS proteins are part of the big family of small GTPases. BRAF is located in chromosome 7q34 and is part of a frequent signaling pathway in solid tumors. KRAS and BRAF are components of the same signaling pathway.

Although very uncommon in breast cancer, KRAS and BRAF mutations are frequently observed in colorectal, pancreatic and lung cancers, as well as melanoma. These mutations seem to be unique to certain molecular types and correlated with prognosis (10,11). Also there are available drugs such as vemurafenib and dabrafenib, that inhibit BRAF and could be used in those breast cancers.

This literature review seeks to show the importance of testing for KRAS and BRAF mutations in certain molecular type of breast cancers for better management of the disease.

METHODOLOGY

Cancer genomes databases were analyzed through bioinformatic portals as Catalogue of Somatic Mutations in Cancer (COSMIC, https://cancer.sanger.ac.uk/cosmic), cBioportal for cancer genomics (https://www.cbioportal.org/) and OncoKB (https://www.oncokb.org/).

PubMed and Google Scholar were employed for searching articles on KRAS and BRAF mutations in human breast cancers, with no language restriction. Published papers were searched using the following keywords and medical subject heading (MeSH) terms: breast cancer; invasive breast cancer; breast carcinoma; invasive breast carcinoma; KRAS mutation and BRAF mutation. The Boolean operators “AND” and “OR” were used to combine 2 or 3 keywords and terms. Studies conducted over the last 10 years that is from 2012 to 2022 were considered for inclusion. The variables studied were the incidence and frequency of KRAS and BRAF mutations, prognostic and predictive values, association with immune tumour infiltration and overall survival (OS).

RESULTS

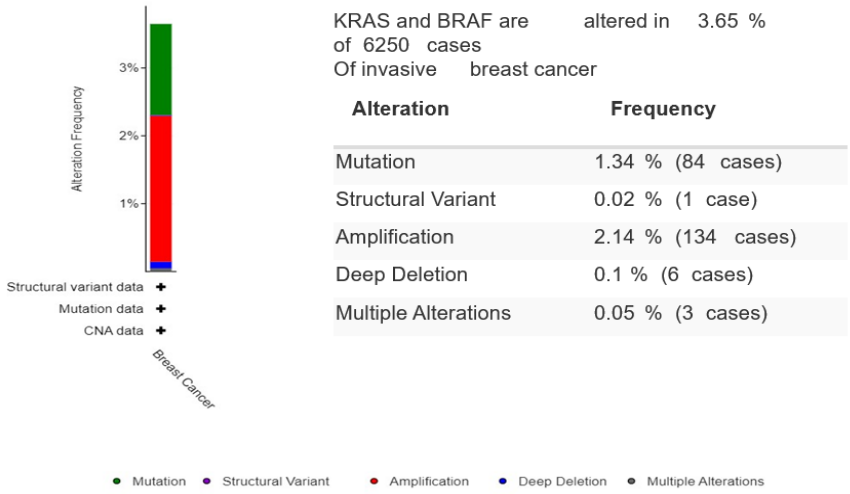
The data included 6395 samples collected from 6109 patients. Among them, there were 6300 cases with genetic alterations, 6250 being exploitable (12-34). There were 5409 samples with copy number alteration and 5213 with both mutations and copy number alteration. The cBioPortal OncoPrint revealed genetic alterations of KRAS in about 2.2% of samples and those of BRAF in 1.9% of samples. Both genes having mostly amplifications than mutations. These mutations were somatic, accounting for 0.7% for KRAS and 0.8% for BRAF.

The phosphatidylinositol-3-OH kinase (PI3K) and RAS signaling pathways are the most commonly encountered in solid tumors in general, and in breast cancer in particular, the former being most affected by genetic alterations. They are essential for the transduction of extracellular signals into intracellular targets. Both pathways can be activated by growth factors or nutrients in the cellular environment. The signals from this activation will thus regulate cell metabolism, cell survival, cell cycle and growth. (6-8,35). Despite their low frequency, knowledge of KRAS and BRAF mutations is useful for improving breast cancer management. as therapies targeting the MAPK/ERK pathway are increasingly developed (8,35,36).

Incidence and frequency of KRAS and BRAF in breast cancers

Genetic alterations and mutations

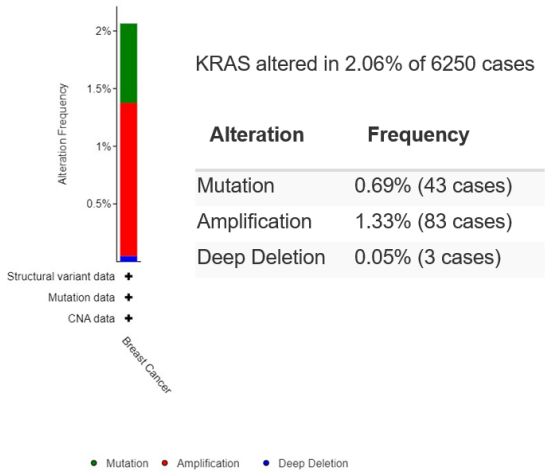
Genetic alterations in BRAF and KRAS occur in 3.65% of the samples studied. Mutations represent 1.34%, amplifications being the major alterations: 2.14% (figure 1).



Alteration	Frequency
Mutation	1.34 % (84 cases)
Structural Variant	0.02 % (1 case)
Amplification	2.14 % (134 cases)
Deep Deletion	0.1 % (6 cases)
Multiple Alterations	0.05 % (3 cases)

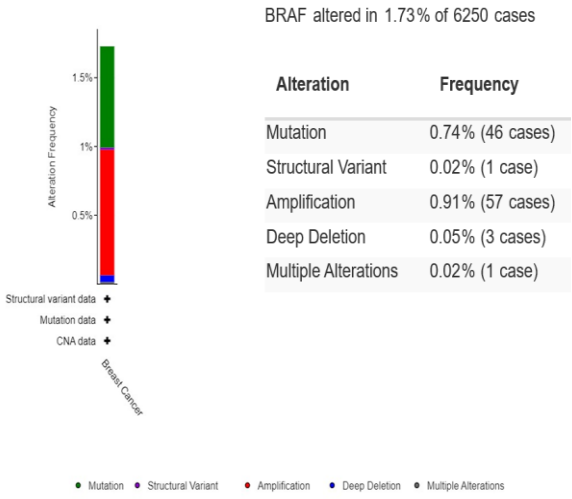
Figure 1: frequency of genetic alterations of BRAF and KRAS in breast

With regard to the alterations of these genes taken separately, mutations in the KRAS gene (0.69%) appear to be less frequent than those in BRAF (0.74%). Furthermore, amplifications are more frequent for KRAS (Figures 2 and 3).



Alteration	Frequency
Mutation	0.69% (43 cases)
Amplification	1.33% (83 cases)
Deep Deletion	0.05% (3 cases)

Figure 2: frequency of KRAS genetic alterations in breast



Alteration	Frequency
Mutation	0.74% (46 cases)
Structural Variant	0.02% (1 case)
Amplification	0.91% (57 cases)
Deep Deletion	0.05% (3 cases)
Multiple Alterations	0.02% (1 case)

Figure 3: frequency of BRAF genetic alterations in breast

These findings confirm the low frequency of these mutations in breast cancer as reported in the literature (7,9). Furthermore, given the small number of KRAS and BRAF gene alterations reported and the type of studies carried out, in particular sequencing on numerous samples, it is difficult to determine the real incidence of these mutations.

Common locus of mutation of KRAS and BRAF

Activation of the RAS signaling pathway in human cancers leads in most cases to alterations in the RAS and BRAF genes. RAS isoforms known to date are KRAS, HRAS and NRAS. Mutations of KRAS and NRAS are the most frequently encountered. Oncogenic mutations in RAS are mainly in the GTPase domain and are categorized into 4 classes: Class I represented by mutations in the G12 isoform; Class II by the G13, K117, and A146 isoforms; Class III by mutations that

affect the function of RAS, namely A59 and Q61 and Class IV where there are very poorly featured mutations distant from the active site of RAS In breast cancer, class I mutations, practically all missense mutations, predominate, with the G12 isoform and its variants G12V/D/A or C depending on the study. (8,35,37,38).

In breast cancer, there is high expression of RAS, compared to benign breast tissue, and grade 3 tumors showed to be associated with mutations of codon 12 of KRAS (39).

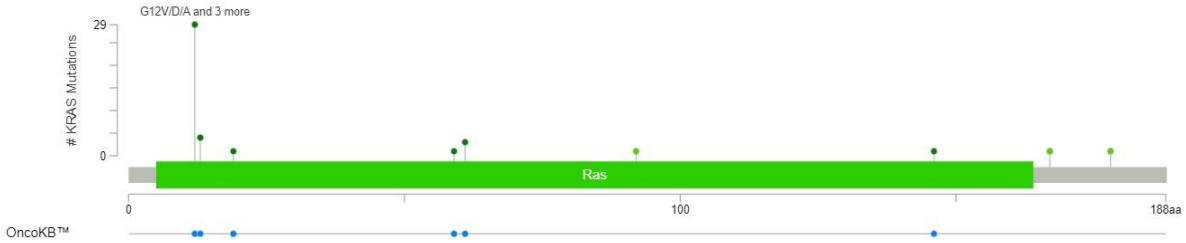


Figure 4: common locus of mutation in KRAS associated with breast cancer. Showing 43 of 46 KRAS mutations in 38 patients / 42 samples. All being missense mutations. The most common locus of mutation is at position G12V/D/A.

Genomic alterations of BRAF are either “activator” or “amplifier”. BRAF mutations are categorized in 3 classes. Class I includes the BRAF V600E mutations and allows the BRAF to act as a constitutively active monomer. Class II mutations allow for constitutively active dimers, they are RASindependent kinase activating dimers, and contain K601E, L597Q, and G469A. Class III BRAF mutations has impaired kinase activity or is inactive. These mutations are located in the P-loop (G466), catalytic loop (N581), or DFG motif (D594, G596). The mutation at aspartic acid 594 (D594) of the DFG motif is a part of the activation loop, and it is the most found in breast cancers according to cBioPortal datas (40, 41) followed by the class I mutation BRAF V600E. The latter are mostly found in most solid tumours, including melanoma, colorectal carcinoma and lung cancer.

These BRAF mutations are less frequent in breast cancer, where they exist, and are more likely to be found at the D594 locus. The D594 mutation differs significantly from the V600E mutation in terms of molecular, pathological, and clinical consequences (40), hence the need to determine the exact nature of these mutations which could have a predictive role in the management of breast cancer.

Prognostic and predictive value of KRAS and BRAF in breast cancer

Although KRAS and BRAF mutations are very uncommon in breast cancer, the RAS/RAF/MEF/ERK signaling pathway is very often activated and these genes amplified, hence the importance of this pathway in tumor progression. Genetic alterations most often affect the KRAS gene and copy number alterations affect both genes (table 1), particularly in triple negative/basal-like breast carcinomas (38). This molecular type is uncommon in the general population and most often affects black women (43–45). Table 1 shows the main RAS/RAF/MEK/ERK pathway driver alterations in primary breast cancer.

In a multivariate study, alteration of RAF was associated with a worse prognosis (28), particularly those with BRAF V600E mutations (47). BRAF D594 mutations are more frequent than BRAF V600E mutations in breast cancer. These mutations belong to two different clusters and are described as having opposite molecular and clinical effects, patients with BRAF D594 mutation having a better prognosis and a longer overall survival than those with BRAF V600E(40,41). In some studies, genomic alterations of BRAF indicate a potential role for immunotherapy in metastatic breast cancer (36) but larger studies are lacking regarding the predictive role of BRAF mutations in breast cancer (48).

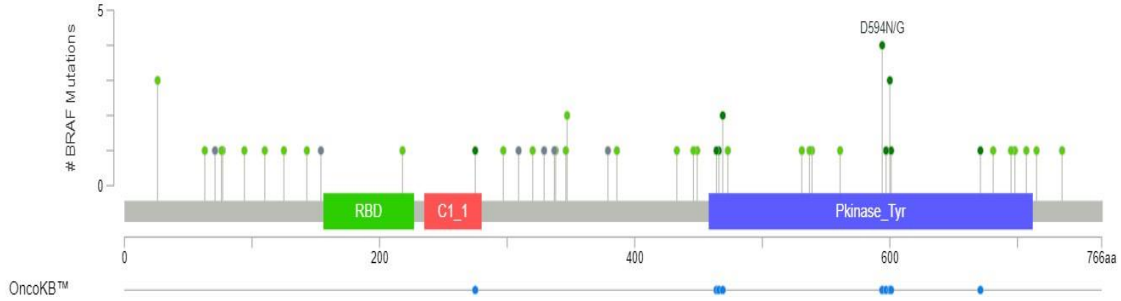


Figure 5: Mutations of BRAF in breast cancer. Somatic mutations on BRAF with aspartic acid Change in breast cancer are mostly seen in D594N/G followed by V600E.

Table 1 : Main RAS/RAF/MEK/ERK pathway genetic alterations in primary breast cancer (38).

Mutations (all types)	Frequency
KRAS	0.6-10%
HRAS	0.2-0.5%
NRAS	0.1%
BRAF	0.6%

According to data on COSMIC, mutations on BRAF are more frequent in HER2 positive and TNBC/basal-like than KRAS mutations are summarized in table 2.

Table 2: KRAF and BRAF mutations in molecular types of breast cancer (38)

	KRAS Mutated/samples (%)	BRAF Mutated/samples (%)
Luminal A	3/349 (0.86%)	4/340 (1.18%)
Luminal B	10/1340 (0.75%)	9/1419 (0.63%)
HER 2	6/241 (2.49%)	20/218 (9.17%)
TNBC*/Basal-like	8/738 (1.08%)	14/698 (2.01%)

**TNBC= triple negative breast cancer.*

Tumor immune infiltration associated with KRAS and BRAF mutations in breast cancer

Cells with a KRAS mutation very often create an immunosuppressive environment, as has been found in several solid cancers namely colorectal, lung, pancreatic and thyroid. The frequency of KRAS mutations is much lower in breast cancer. Often associated with rapid progression and poor prognosis in above cancers, KRAS mutations are expected to be responsible for rapid tumor progression and decreased tumor immune micro environment. According to ER, PR and HER2 status, KRAS mutations are found to be more frequent in triple negative breast cancer, which are more often grade 3 tumors, than luminal A and B cancers, it is noteworthy that in luminal B cancers, there is an alteration in the RAS signaling pathway in 62% of cases. In some studies, KRAS mutations occur more often in TNBC and HER2 to a lesser extent. It is associated with a good tumor micro environment. In addition, it seems to be associated with a better prognosis, improved disease-free survival and overall survival (49).

Concerning BRAF mutations in breast cancer, the amplification of the expression of this gene is approximately 30% and it is most often in TNBC (11). As the role of this gene in breast cancer is not yet well known. Some studies suggest that activation of certain BRAF segments is necessary for the initiation and progression of breast cancer, as well as for the occurrence of metastasis. In the latter, a high tumor mutational burden (TMB) is observed, which would be a potential biomarker for immune check point inhibitors (ICPI) (48).

These data from the literature are consistent with those from public databases where there is a significant association between overall survival and KRAS and BRAF mutations in breast cancer, with BRAF mutated having a better OS (50).

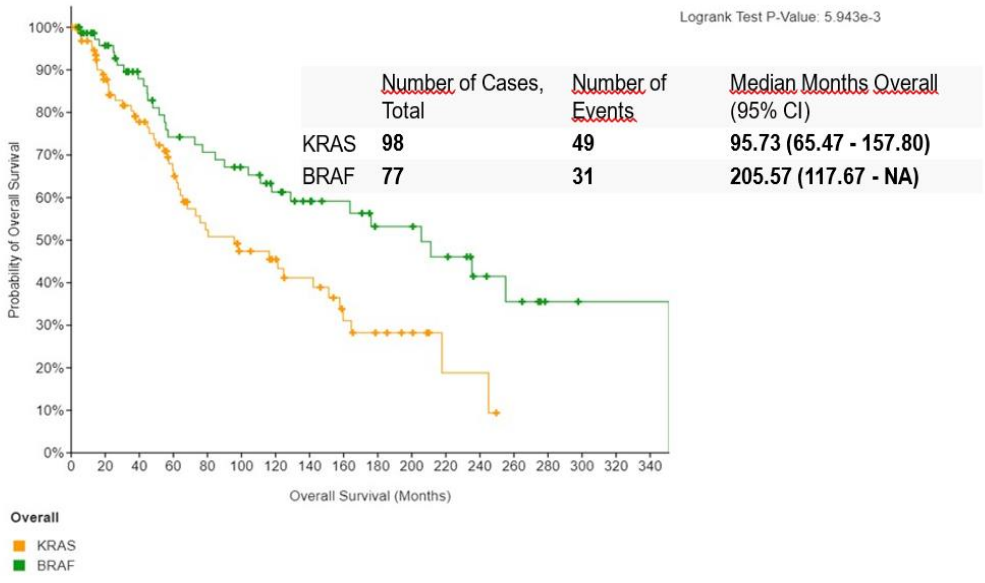


Figure 6: probability of overall survival according to the BRAF (115samples with alterations/113 patients) and KRAS (141samples with alterations/136 patients) status in breast cancer. q-value: 0.0297. p-value: 5.943e-3, Log Rank test.

DISCUSSION

Although infrequent and under-researched, alterations in the BRAF and KRAF genes, most specifically mutations, are effective in breast cancer. Studies on these mutations are infrequent and sporadic, which makes it impossible to determine their effective incidence. RAS gene expression is increased in breast cancer compared to normal breast tissue or benign tumors (40). In KRAS,

the most found locus of mutation is G12, as in other malignant tumors where KRAS is mutated (40,41). In contrast, the locus V600E which is the most encountered in the other cancers with BRAF mutation, is less represented than D594. These two loci belongs to class I and class II respectively and have opposite molecular, pathological, and clinical consequences, V600E being associated to a worse clinical course than D594, Hence the importance of further research into these mutations (40,12-34). Both KRAS and BRAF mutations are most frequently linked to triple negative and to some extend HER 2 positive breast cancer than in the other molecular types (38,40,46,47). The former is more common in black women (43-45). Concerning the prognosis and the overall survival, breast cancers with BRAF mutations are more related to a better prognosis and overall survival than those with KRAS mutations, this not only because of the large number of BRAF mutations on locus D594, but also because of the association with a good tumor immune micro environment (14,40,41). These breast cancers with KRAS and BRAF mutations in some studies are associated with a better prognosis, an improved disease-free survival and an overall survival. The presence of high mutational burden observed implies that they would be potential biomarkers for immune check point inhibitors (11,48-50).

CONCLUSION

Although infrequent and under-researched, mutations in the BRAF and KRAF genes are effective in breast cancer. They are most often linked to triple negative breast cancer. The latter is more common in black women. Larger studies on mutations in these two genes in this subpopulation could help to understand and improve the management of this disease in this group. Furthermore, they seem to be predictive factors and potential biomarker for immune check point inhibitors. They are also linked to a good prognosis and overall survival, BRAF mutations having a better overall survival than KRAS mutations.

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