



## PDL1 Expression as a Prognostic Factor in Female Patients with Invasive Breast cancer

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**Abstract:** In relation to the apoptosis program, programmed death 1 ligand 1 (PD-L1) has been named as a programmed cell death-1 receptor. There is growing indication of a dynamic crosstalk among the breast tumor and immune system. The existence of regulatory T cells in peripheral blood in addition to the cancers of breast tumor patients are documented in many advanced studies. So, we aimed in this study to evaluate PDL1 as a prognostic factor in relation to other clinicopathological factors and survival. **Patients and Methods:** This retrospective study was performed at Clinical Oncology Department, Tanta University Hospital, within Jun 2011 and Jun 2016 on one hundred and sixty three (163) female breast cancer patients with histopathologically confirmed invasive ductal carcinoma. Patient's data were recorded. Specimens from affected lesions of breast tissues were fixed in formalin and processed for histopathological examination after staining with IHC for PD-L1. **Results:** PDL1 expression was significantly connected with N stage, hormonal levels, lymphovascular invasion, grade of tumor (p), tumor size, molecular subtypes and menopausal status. The 5-years OS owing to PDL1 expression was 50.1% for positive expression and 72.6% for negative expression ( $p < 0.001$ ). The 5-years DFS according to PDL1 expression was 22.4% for positive expression and 77.9% for negative expression ( $p < 0.001$ ). The results revealed to a significant 5-years OS rate with PDL1 expression and age in multivariate analysis. The 5-years DFS showed significant correlation with PDL1 expression, nodal status, hormonal status and Ki67 expression. **Conclusion:** PDL1 expression was significantly associated with N stage, hormonal levels, lymphovascular invasion, grade of cancer, tumor size, molecular subtypes and menopausal status. PDL1 expression was independent prognostic factors for invasive breast carcinoma and therefore can be considered as independent indicator for bad prognosis and can be used as goal for the discovery of novel treatments.

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**Keywords:** PDL1; Expression; Prognostic; Factor; Female; Patient; Invasive Breast cancer

### 1. Introduction

Breast tumor is the more usually diagnosed tumor and the main etiology of morbidity and mortality in women in the world [1]. In the few past decades the frequency of breast tumor has elevated progressively, as a result of the great advances achieved in the treatment of breast cancer, the mortality due to breast cancer seemed to be diminishing [2-3].

Programmed death 1 ligand 1 (PD-L1) is an immunoglobulin superfamily haplotype type I transmembrane glycoprotein, which has been named as a programmed cell death-1 receptor in relation to the apoptosis program. [1] Human PD-1 gene, also known as CD279, was located in the chromosome 2q37.35 with relative molecular weight of 55 kDa and composed of extracellular domain, transmembrane domain, and intracellular domain. [2] PD-L1 was widely expressed on the surface of B lymphocytes, monocytes, natural killer cells, macrophages, and

vascular endothelial cells. It was also upregulated in human tumor cell lines, such as ovarian cancer, lymphoma, and malignant melanoma, indicating a close relationship with the occurrence and development of tumors. [3] The expression of PD-L1 in various tissue specimens has been studied, such as colon cancer, [4] malignant melanoma, [5,6] nonsmall cell lung cancer, renal cell carcinoma, and esophageal cancer. [7,8]

There is increasing indication of a dynamic crosstalk among the breast cancer and immune system in spite of the breast tumor is usually assumed to be less immunogenic than RCC or melanoma. Recently, regulatory T cells were recorded in the breast tumors tissue and in peripheral circulation of patients [9, 10]. Moreover, PD-L1 is expressed on breast cancer cells while, inhibitory molecules of the CD28 receptor

family are up regulated on breast tumor-specific T cells [11–13].

So, we aimed in this study to evaluate PDL1 as a prognostic factor in relation to other clinicopathological factors and survival.

## 2. Patients and Methods

The current work (retrospective study) was performed at carried out at Tanta University Hospital, Department of Clinical Oncology, at the period from Jun 2011 to Jun 2016 on one hundred and sixty three (163) female breast cancer patients with diagnosed and confirmed as invasive ductal carcinoma by histopathological examination. Various parameters concerning the patients were obtained involving; clinical symptoms, menopausal status, age, pathology, tumor size (T), tumor grade (G), number of previous excisions and lymphovascular invasion (LVI), invaded axillary lymph nodes (N), progesterone receptors (PR), Estrogen receptors (ER), Her-2neu expression status and Ki67 expression. Complete blood profile, blood chemistry tests (kidney and liver functions tests), Imaging studies (abdominopelvic ultrasound, Chest X-ray, MRI, CT, and scan of bone were performed.

### PDL1 expression

Specimens of tissues were obtained from the breast lesion and fixed in formalin, paraffin-embedded and processed for immunohistochemical technique which done in the department of Pathology, Tanta University Hospital.

### Evaluation of PDL1 Immunostainin

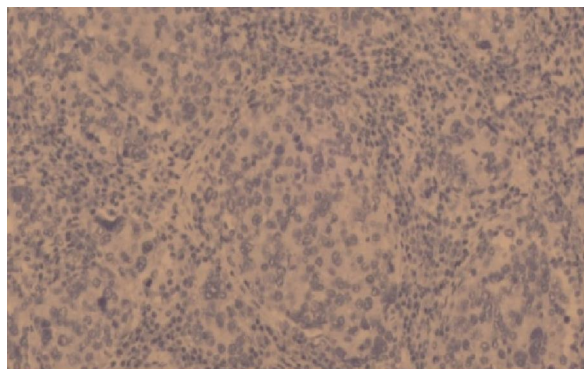


Fig A: invasive ductal carcinoma showed negative expression of PDL1[X400]

Staining for PD-L1 by using immunohistochemistry (IHC) technique was carried out in 3  $\mu$ m sections from paraffin blocks. In this technique an anti-human PD-L1 rabbit monoclonal antibody was used as the primary antibody. The

procedures of IHC were performed according to the instructions of manufacturers of the IHC kit. Positive (human tonsil) and negative staining were done in corresponding to the paraffin sections. Positivity for PDL-1 marker was determined depending on the following criteria: cytoplasmic and membranous staining  $\geq 1\%$  in tumour cells and graded according to intensity of staining of tumor cells into mild [+1] moderate [+2] and strong [+3]

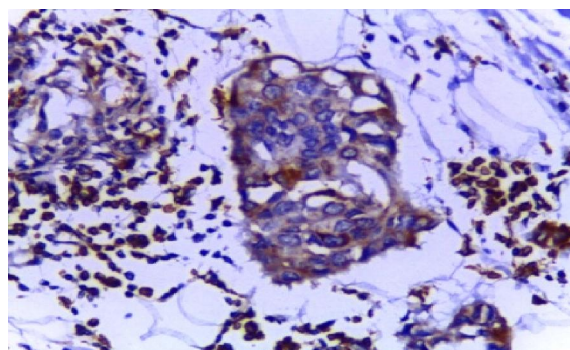


Fig B: invasive ductal carcinoma showed strong expression of PDL1[X400]

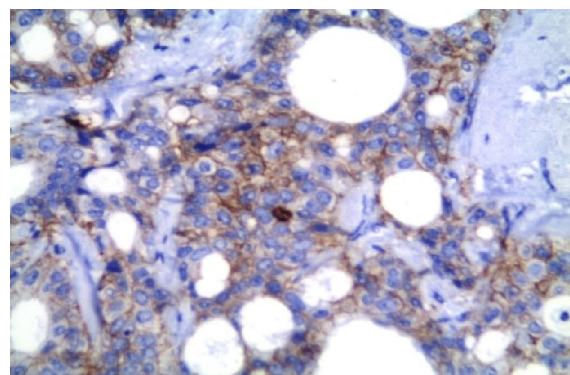


Fig C: invasive ductal carcinoma showed moderate expression of PDL1[X400]

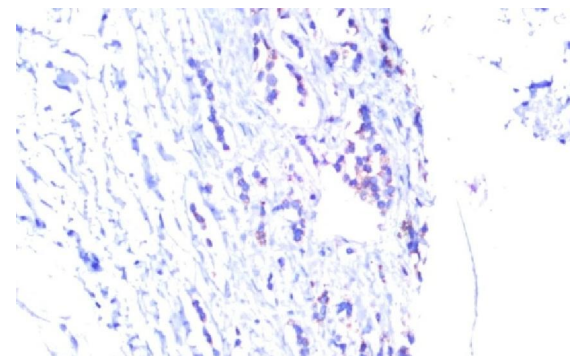


Fig D: Invasive lobular showed mild expression of PDL1[X400]

### Statistical analysis

Statistical Package for the Social Sciences, version 21.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis of all data. Chi-square test was applied for estimation of the correlation among PDL1 expression and clinicopathological features. An independent prognostic factors for Overall survival was determined by using univariate and multivariate analyses. The Kaplan-Meier method was used for estimation of overall survival (OS), and the log-rank test was used analyzing the differences in survival rates. P value less than 0.05 was considered to be significant statistically.

### 3. Results

The current investigation assessed an invasive ductal breast carcinoma patients (163 women), their ages averaged  $50.4 \pm 11.41$  years, and ranged from 24 to 75 years, while the follow up period extended from 5 to 8 years. PDL1 expression was significantly correlated with N stage ( $p < 0.02$ ), hormonal status ( $p = 0.005$ ), tumor grade ( $p < 0.005$ ), lymphovascular invasion ( $p < 0.007$ ), tumor size ( $p < 0.001$ ), molecular subtypes ( $p < 0.001$ ) and menopausal status ( $P = 0.04$ ) as demonstrated in **Table (1)**. Though, the statistical analysis not revealed to a significant connection with age ( $p = 0.12$ ), Her-2 expression ( $p = 0.81$ ) and tumor pathology ( $p = 0.13$ ). The 5-years overall survival (OS) and Disease free survival (DFS) in all cases were averaged 63.4% and 56.1%, respectively (Figs. 2 & 3). **Figure (1)** revealed that the 5-years OS between all patients according to PDL1 expression was 50.1% for positive expression and 72.6% for negative expression ( $p < 0.001$ ). The 5-years DFS between all patients rendering to PDL1 expression was 22.4% for positive expression and 77.9% for negative expression ( $p < 0.001$ ) (**Fig. 2**). By applying univariate analysis, there was significant impact on 5-year OS rate with T stage ( $p = 0.004$ ), PDL1 ( $p < 0.001$ ), hormonal status ( $p = 0.024$ ), N stage ( $p = 0.038$ ), lymphovascular invasion ( $p = 0.007$ ), Ki67 ( $p = 0.001$ ), molecular subtypes ( $P = 0.01$ ) and age ( $p < 0.001$ ) as tabulated in table (2). Menstrual status, pathology, grade and Her/2-neu showed insignificant correlation with 5 year OS rate as P -value for them was ( $p = 0.106$ ), ( $p = 0.115$ ), ( $p = 0.415$ ) and ( $p = 0.598$ ) respectively. A significant effect on 5-year DFS rate with Tumor size ( $p = 0.04$ ), N stage ( $p < 0.001$ ), Hormonal status ( $p = 0.012$ ), Her-2/neu ( $p = 0.028$ ), lymphovascular

invasion ( $p = 0.025$ ), Age ( $p = 0.007$ ), Ki67 ( $p < 0.001$ ) and molecular subtypes ( $p < 0.001$ ), while menstrual status, pathological type and grade of differentiation showed insignificant correlation with 5 year DFS rate as P -value for them was ( $p = 0.27$ ), ( $p = 0.477$ ) and ( $p = 0.06$ ) respectively, as estimated by the univariate analysis (Table3). In multivariate analysis, (Table 3), there was significant 5-years OS rate with PDL1 expression ( $p = 0.014$ ) and age ( $p < 0.038$ ). multivariate analysis, (Table 3) according to 5-years DFS showed significant correlation with PDL1 expression ( $p < 0.001$ ), Nodal status ( $p < 0.001$ ), hormonal status ( $p = 0.023$ ) and Ki67 expression ( $p < 0.001$ ).

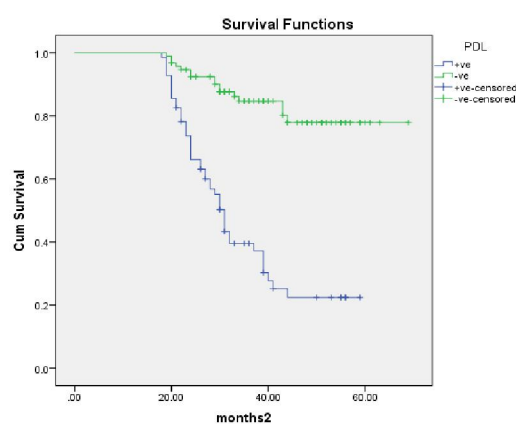


Fig. (1) Disease free survival

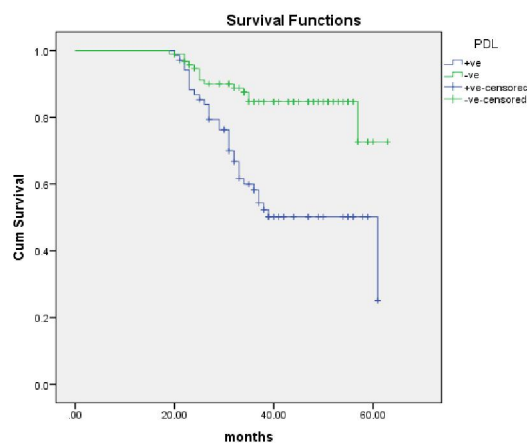


Fig. (2) Overall survival

**Table (1): Patient characteristics according to PDL1 expression**

		<b>PDL1-ve n = 94 (57.67%)</b>	<b>PDL1+ve n = 69 (42.33%)</b>	<b>P</b>
<b>Age</b>				
≤50	62(38%)	31(33%)	31(44.9%)	0.12
>50	101(62%)	63(67%)	38(55.1%)	
<b>Pathology</b>				
Ductal	144(88.3%)	80(85.1%)	64(92.8%)	0.13
Lobular	19(11.7%)	14(14.6%)	5(7.2%)	
<b>Menopause</b>				
Pre	72(44.2%)	35(37.5%)	37(53.6%)	0.04*
Post	91(55.8%)	59(62.5%)	32(46.4%)	
<b>N</b>				
<b>N0</b>	69 (42.3%)	47(50%)	22(31.9%)	0.02*
<b>N+ve</b>	94 (57.7%)	47(50%)	47(68.1%)	
<b>Grade</b>				
G1 & 2	118(72.4%)	76(80.9%)	42(60.9%)	0.005*
G3	45(27.6%)	18(19.1%)	27(39.1%)	
<b>LVI</b>				
Non	100(61.3%)	66(70.2%)	34(49.3%)	0.007*
Yes	63(38.7%)	28(29.8%)	35(50.7%)	
<b>radiotherapy</b>				
Yes	68(78.2%)	12(52.2%)	56(87.5%)	<0.001
No	19(21.8%)	11(47.8%)	8(12.5%)	
<b>Ki67</b>				
Low	51(31.3%)	40(42.6%)	11(15.9%)	<0.001*
High	112(68.7%)	54(57.4%)	58(84.1%)	
<b>Her-2</b>				
Positive	35(21.5%)	20(20.8)	15(22.4%)	0.81
Negative	128(78.5%)	76(79.2%)	52(77.6%)	
<b>Tumor size</b>				
≤5	101(62%)	69(73.4)	32(46.4)	<0.001*
>5	62(38%)	25(26.6)	37(53.6)	
<b>Hormonal status</b>				
+ve	120(73.6)	77(81.9)	43(62.3)	0.005*
-ve	43(26.4)	17(18.1)	26(37.7)	
<b>Luminal A</b>	47(28.8)	9(13)		0.001*
<b>Luminal B</b>	76(46.6)	37(53.6)		
<b>Her-2 +ve</b>	18(11)	11(15.9)		
<b>Triple -ve</b>	22(13.5)	12(17.4)		

**Table (2): Univariate and multivariate analysis of factors affecting Overall Survival rate**

Factor	Univariate analysis according to OS	P	HR (95% CI)	p-value
<b>Age</b>				
≤50 years	53.2	<b>&lt;0.001</b>	0.494 (0.254-0.961)	0.038
>50 years	79.7			
<b>Pathology</b>				
Ductal Ca.	61.3	0.115		
Lobular Ca.	88.5			
<b>N stage</b>				
Negative	78.2	<b>0.038</b>	1.231 (0.918 – 1.649)	<b>0.165</b>
Positive	50.9			
<b>Menopausal status</b>				
Pre-	61.3	0.106		
Post-	75.8			
<b>LVI</b>				
-ve	77.5	<b>0.007</b>	1.162 (0.575-2.349)	0.676
+ve	57.4			
<b>Her-2/neu status</b>				
+ve	62.2	0.598		
-ve	64.5			
<b>Tumor size</b>				
< 5	79.3	0.004	0.900 (0.408 – 1.986)	0.795
≥ 5	27.3			
<b>Grade</b>				
1-2	58.9	0.415		
3	66.1			
<b>Hormonal Status</b>				
Positive	65.9	0.024	1.531 (0.702 – 3.339)	<b>0.284</b>
negative	56.0			
<b>PD-L1</b>				
+v	50.1	<b>&lt;0.001</b>	0.408 (0.200 – 0.833)	<b>0.014</b>
-ve	72.6			
<b>Ki67</b>				
Low	79.4	<b>0.001</b>	2.403 (0.803-7.189)	0.117
high	60.0			
<b>Molecular subtypes</b>				
Luminal A	77.4	0.01	0.876 (0.536 – 1.433)	0.599
Luminal B	64.9			
Her-2/neu +ve	53.3			
Triple - ve	57.9			

**Table (3) Univariate & multivariate analysis of factors affecting Disease free Survival rate**

Factor	Univariate analysis according to DFS	P	HR (95% CI)	p-value
<b>Age</b>				
≤50 years	41.3	<b>0.007</b>	0.656 (0.363-1.187)	0.164
>50 years	61.6			
<b>Pathology</b>				
Ductal Ca.	53.0	0.477		
Lobular Ca.	63.2			
<b>N stage</b>				
Negative	64.6	<b>&lt;0.001</b>	1.677 (1.282 – 2.193)	<b>&lt;0.001</b>
Positive	45.9			
<b>Menopausal status</b>				
Pre-	48.7	0.27		
Post-	58.1			
<b>LVI</b>				
-ve	58.2	<b>0.025</b>	0.852 (0.468-1.549)	0.599
+ve	48.3			
<b>Her-2/neu status</b>				
+ve	33.7	0.028	0.819 ( 0.444 – 1.513)	<b>0.524</b>
-ve	58.7			
<b>Tumor size</b>				
< 5	58.6	0.044	0.575 (0.293 – 1.126)	0.107
≥ 5	47.1			
<b>Grade</b>				
1-2	60.5	0.06		
3	41.0			
<b>Hormonal Status</b>				
Positive	64.3	0.012	2.260 ( 1.120 – 4.559)	<b>0.023</b>
negative	33.4			
<b>PD-L1</b>				
+v	22.4	<b>&lt;0.001</b>	0.202 (0.107 – 0.384)	<b>&lt;0.001</b>
-ve	77.9			
<b>Ki67</b>				
Low	78.4	<b>&lt;0.001</b>	5.949 (2.311-15.317)	<b>&lt;0.001</b>
high	41.3			
<b>Molecular subtypes</b>				
Luminal A	81.9	<b>&lt;0.001</b>	0.734 (0.488 – 1.102 )	0.136
Luminal B	47.9			
Her-2/neu +ve	29.6			
Triple - ve	32.4			

#### 4. Discussion

In this study, one hundred and sixty three female patients with invasive ductal carcinoma of the breast were evaluated and PDL1 expression was expressed in 42.3% of all patients. Triple negative had higher incidence (12/22 patients, 54.5%). Positive expression of PDL1 was correlated significantly with N stage ( $p<0.02$ ), hormonal status ( $p=0.005$ ), tumor grade ( $p<0.005$ ), lymphovascular invasion ( $p<0.007$ ), tumor size ( $p<0.001$ ), molecular subtypes ( $p<0.001$ ) and menopausal status ( $P=0.04$ ). Whereas, there was a non-significant association with tumor pathology

( $p=0.13$ ), age ( $p=0.12$ ) and Her-2 expression ( $p=0.81$ ). The 5-years Disease free survival (DFS) and overall survival (OS) rates obtained from all women in the study were averaged 56.1% and 63.4%, respectively.

The 5-years OS within all diseased women depending on PDL1 expression was averaged 50.1% for positive expression and 72.6% for negative expression ( $p<0.001$ ). While, the 5-years DFS within all diseased women basing on PDL1 expression was averaged 22.4% for positive expression and 77.9% for negative expression ( $p<0.001$ ).

There was a significant effect by using univariate analysis, on 5-year OS rate with N stage ( $p=0.038$ ), T stage ( $p=0.004$ ), PDL1 ( $p<0.001$ ), hormonal status ( $p=0.024$ ), lymphovascular invasion ( $p=0.007$ ), Ki67( $p=0.001$ ), molecular subtypes ( $P=0.01$ ) and age ( $p<0.001$ ). Menstrual status, pathology, grade and Her/2-neu demonstrated a non-significant relationship with 5 year OS rate as  $P$  -value for them was ( $p=0.106$ ), ( $p=0.115$ ), ( $p=0.415$ ) and ( $p=0.598$ ) respectively. Meanwhile, univariate analysis showed a significant impact on 5-year DFS rate with Tumor size ( $p=0.04$ ), N stage ( $p<0.001$ ), Hormonal status ( $p=0.012$ ), Her-2/neu ( $p=0.028$ ), lymphovascular invasion ( $p=0.025$ ), Age ( $p=0.007$ ), Ki67 ( $p<0.001$ ) and molecular subtypes ( $p<0.001$ ), while menstrual status, pathological type and grade of differentiation presented an on-significant link with 5 year DFS rate ( $p=0.27$ ,  $p=0.477$  and  $p=0.06$  respectively).

In multivariate analysis for 5-years OS rate there was significant correlation with PDL1 expression ( $p=0.014$ ) and age ( $p<0.038$ ). multivariate analysis, according to 5-years **DFS showed significant correlation with** PDL1 expression ( $p<0.001$ ), **Nodal status** ( $p<0.001$ ), hormonal status ( $p=0.023$ ) and Ki67 expression ( $p<0.001$ ).

Some studies showed that patients with positive lymph node metastasis, ER- negativity and higher histological grades have a tendency to increase in the levels of expression of PD-L1 than patients without metastasis in lymph nodes, ER-positivity and lesser histological grades. Also, PD-L1 was expressed more commonly in TNBC than in non-TNBC and their findings reveal that rise in PD-L1 expression may be a prognostic marker for decreased OS (Zhang et al., 2017).

Muenst et al 2014 evaluated 650 breast cancer specimens and PD-L1 was expressed in 152 (23.4 %), expression was significantly correlated with tumor size, age, tumor grade, AJCC primary tumor classification, high Ki-67 expression, lymph node status and absence of ER expression. PD-L1 expression was associated with a significantly worse OS by using univariate analysis. Whereas, PD-L1 expression remained an independent negative prognostic factor for OS when multivariate analysis was applied. Expression of PD-L1 was correlated significantly with worse OS in the luminal B HER2(+ve) subtype, in the luminal B HER2(-ve) subtype, the basal-like subtype and the HER2 subtype, by applying subset analyses.

Fei et al., 2018, investigated 112 patients with invasive breast cancer and they found that the positive expression of PD-L1 was not related with the patients' age, menopause history, family history of breast cancer, tumor size, and location of the tumor ( $P>0.05$ ) while it was related with lymph node metastasis, the

clinic staging, and histopathological grading ( $P<0.05$ ).

Zhou et al., 2018 examined 136 patients with invasive breast cancer for the expression of PD-L1. The expression of PD-1 was associated with the expression of progesterone and estrogen receptors, the histological grade and Ki-67 ( $P<0.05$ ). The positive expression rates of PD-1 and PD-L1 were averaged 43.5% and 47.8 in triple-negative breast cancer (TNBC), which were higher than other subtypes ( $P<0.05$ ). Regarding breast invasive ductal carcinoma, the expression of PD-L1 in tumor cells was established to be an independent prognostic risk factor with the progression-free survival rate ( $P=0.003$ ).

### Conclusion

PDL1 expression was significantly associated with tumor grade ( $p$ ), hormonal status, N stage, tumor size, lymphovascular invasion, molecular subtypes and menopausal status. For invasive breast carcinoma, PDL1 expression was not considered dependent prognostic factors. Therefore PDL1 can be applied as independent indicator for bad prognosis and can be used as target for the development of novel treatments. Additional investigate numbers of patients are required.

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