

## Gene prioritization, communality analysis, networking and metabolic integrated pathway to better understand breast cancer pathogenesis

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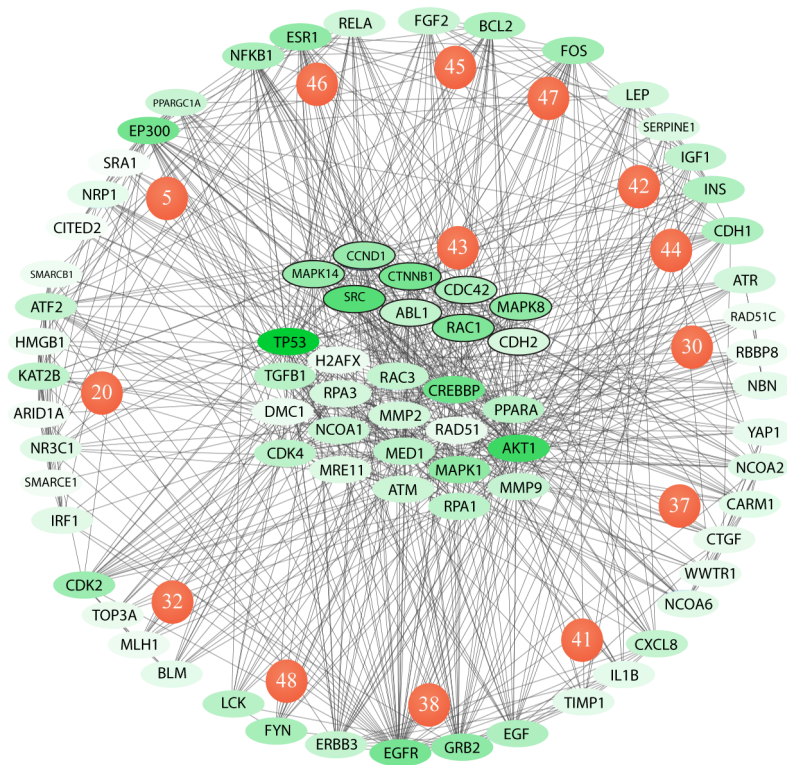
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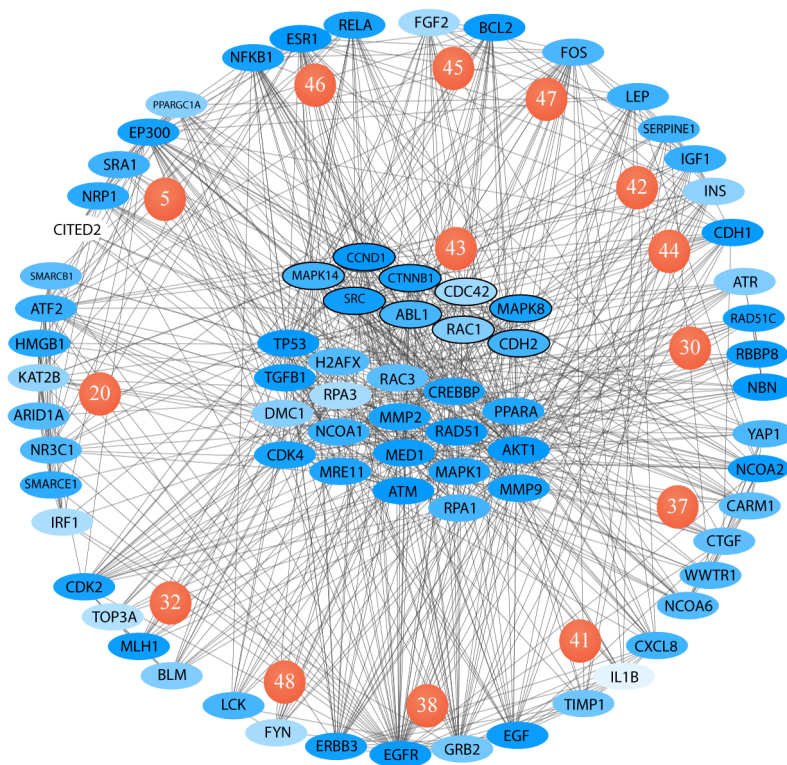
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## Supplementary Figure S1

a.

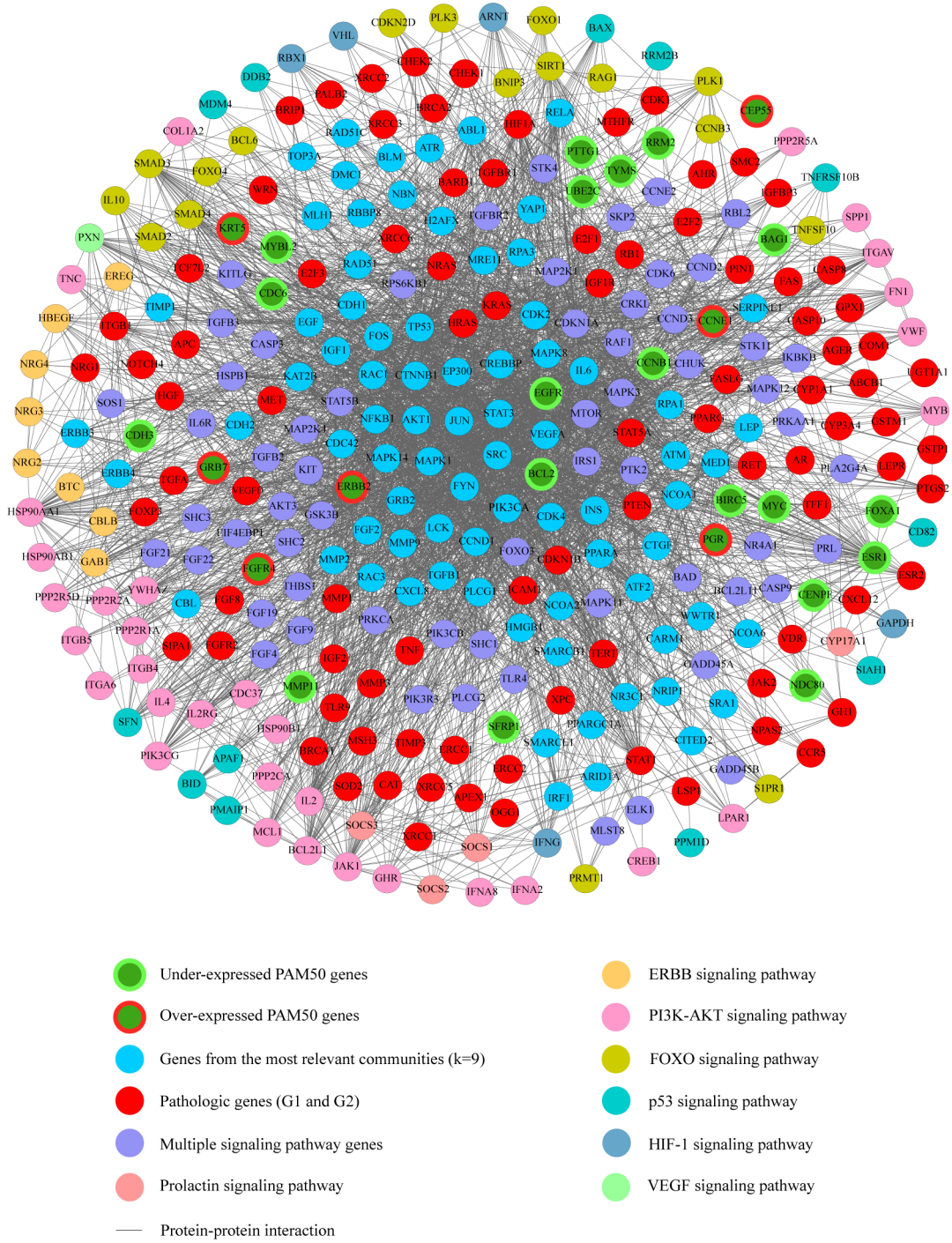


b.



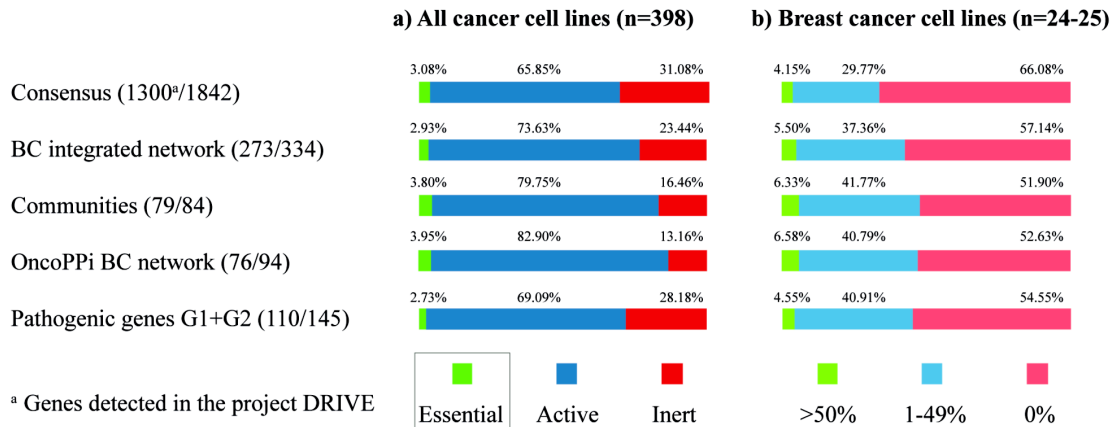
**Supplementary Figure S1 | (a)** Gradient connectivity degree of genes from most relevant communities. **(b)** Gradient ranking distribution of genes from most relevant communities.

# Supplementary Figure S2

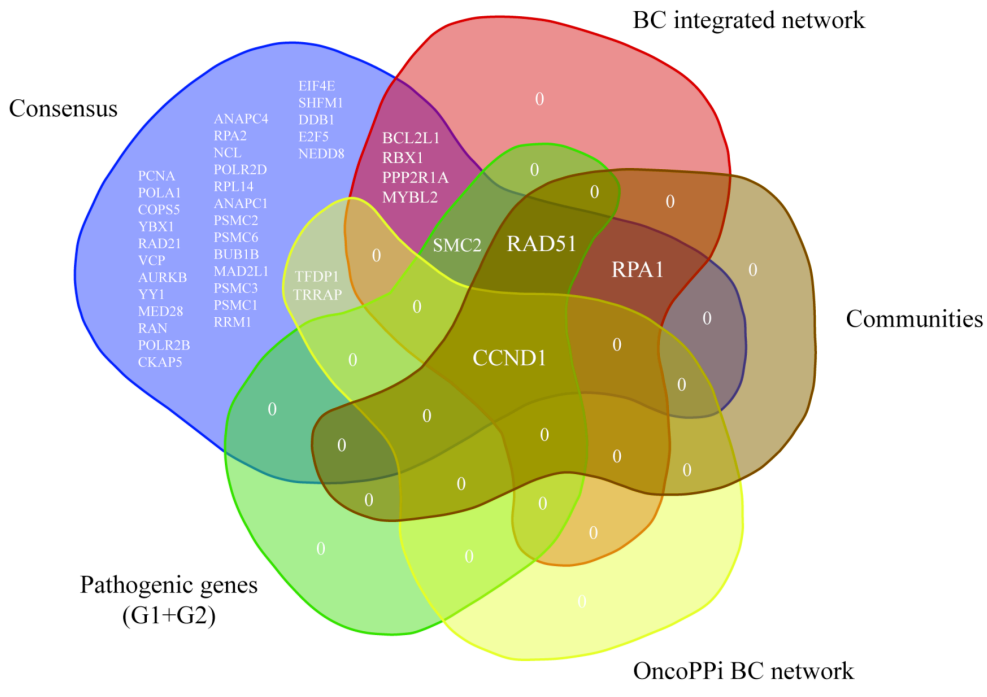


Supplementary Figure S2 | Breast cancer integrated network.

**Supplementary Figure S3**

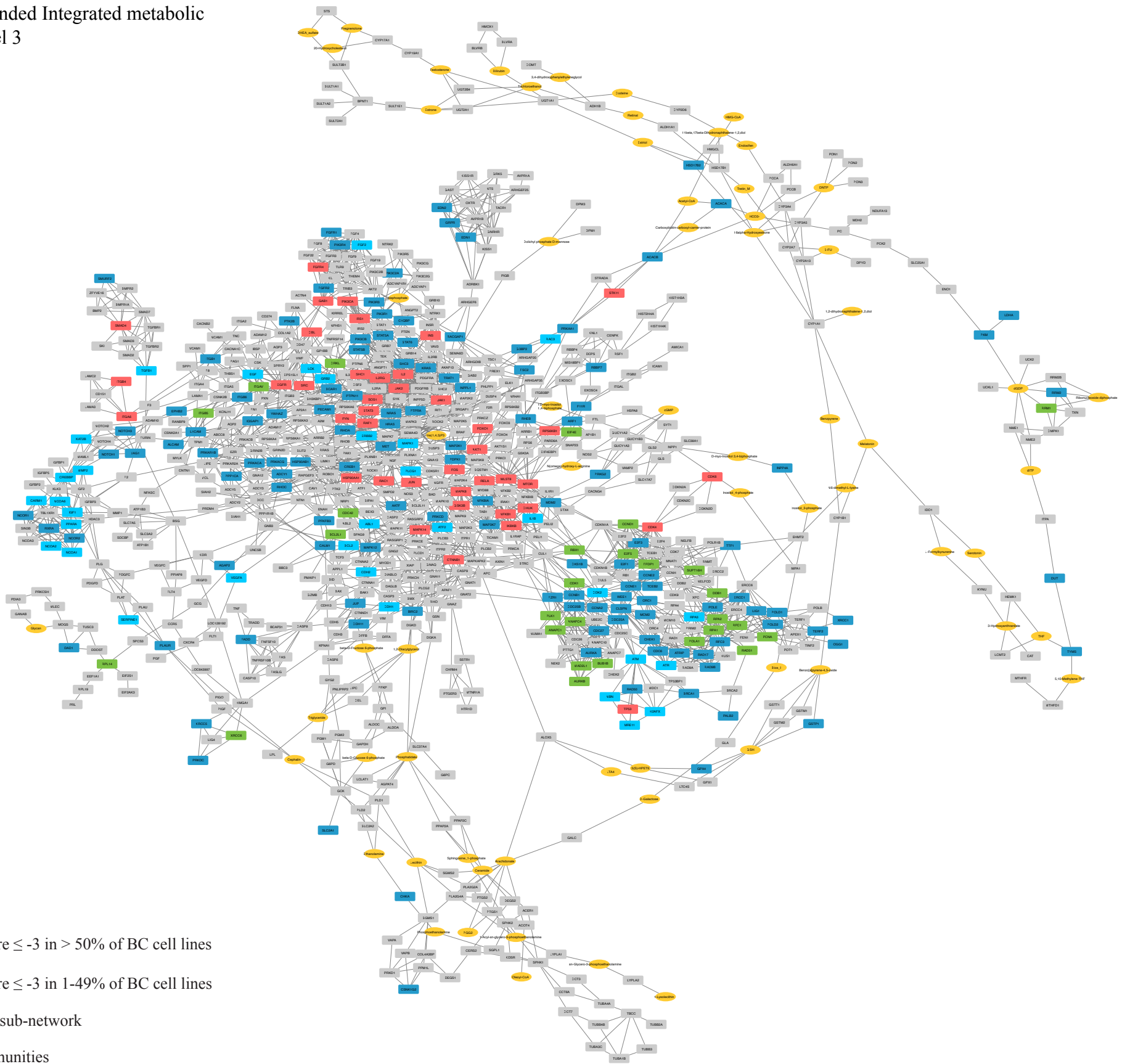


**c) Venn diagram of essential genes ( $\leq -3$ ) in > 50% of BC cell lines**



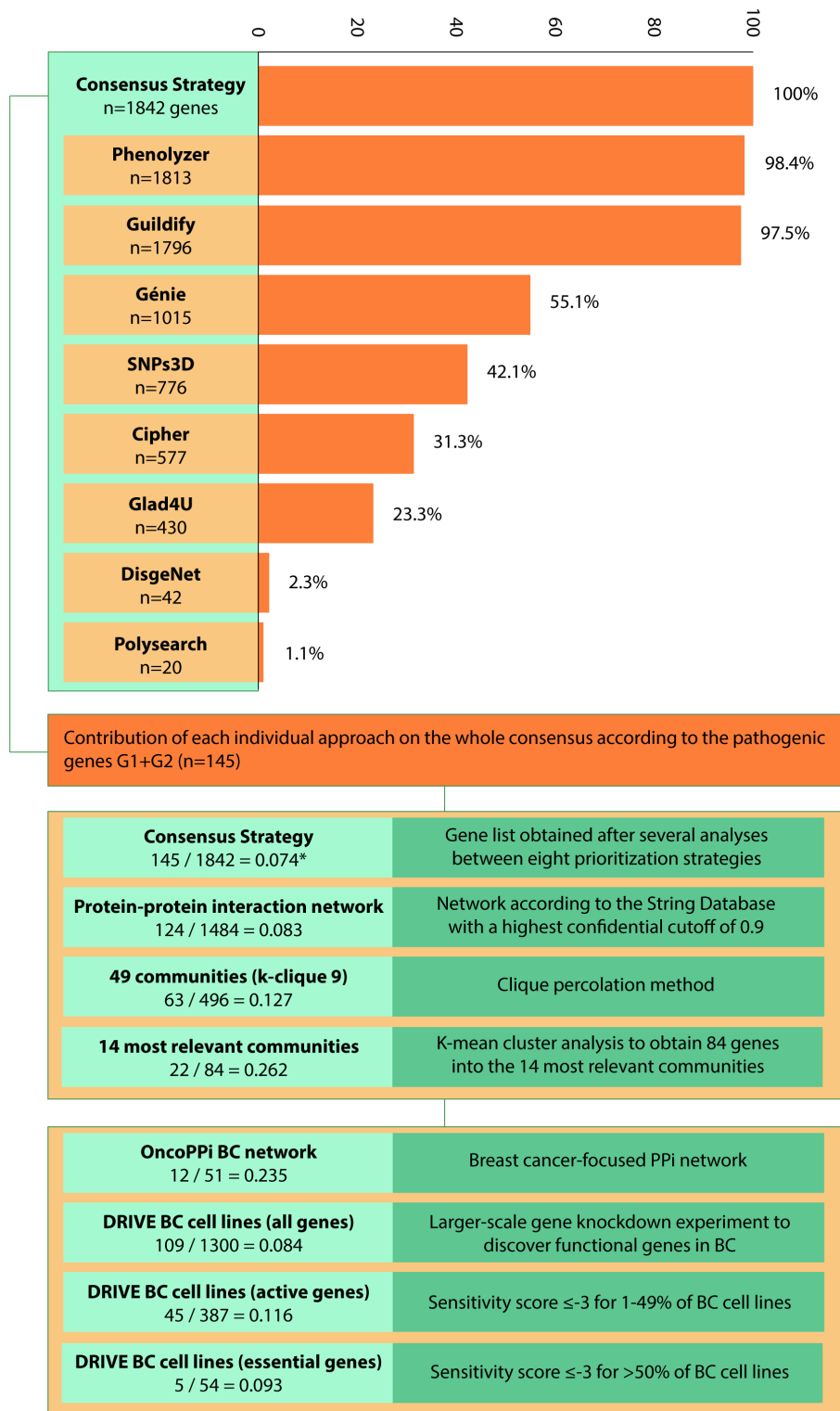
**Supplementary Figure S3 | Venn diagram of the essential genes in all cancer cell lines.**

**Supplementary Figure S4 | Expanded Integrated metabolic network corresponding with Model 3**



- Compounds
- DRIVE: Genes with sensitivity score  $\leq -3$  in  $> 50\%$  of BC cell lines
- DRIVE: Genes with sensitivity score  $\leq -3$  in 1-49% of BC cell lines
- Genes from OncoPPi breast cancer sub-network
- Genes from the most relevant communities

## Supplementary Figure S5



\* Pathogenic genes G1+G2 / genes per approach = ratio

Supplementary Figure S5 | Contribution of each individual approach on the whole consensus

**Table S1.** Identification of pathogenic genes. Gene knockout in animal models (Group 1)

PRIMARY GENE	SECONDARY GENE	REFERENCE	OBSERVATIONS
TP53		1	
BRCA1	TP53	2	
TIMP3	TNF	3	tumor promotion and suppression effects of this gene
ESR1	WNT1	4	ER gene
PTEN	PKB, AKT	5	
ERK5		6	
MSF		7	Septin 9 (MSF)
AKT1		8	
COX2	ERBB2	9	
TFF1		10	
CX26		11	GJB2
ERBB2		12	
AR		13	
ATM		14	
MET		15	
WNT1	FGF-3	15	
NOTCH4	TGF-b	15	
KRAS		15	RAS family
NRAS		15	RAS family
HRAS		15	RAS family
HGF		15	
IGF2		15	
MYC		16	
LPA		16	
STAT5A		16	
INT3		16	
RB		16	RB/p107
APC		16	
ATX		16	ATXN1
STAT1		16	
PDK1		16	
CCND1		17	
FGF		17	FGF-1
BRCA2	p53, Bub1, Mad3L	18	
IGF1R	KRAS	19	
PIN1		20	
TGFA	p53, MYC, STAT5A	21	
TGFB1		21	
FGF3	WNT1	21	
FGF7		21	

FGF8		21	
NRG1	MYC	21	NDF
IGF1		21	
SRC		21	
RET		21	
CDK1		21	
CCNE1		21	
MDM2		21	
ITGB1		22	
JAK2	STAT5	23	
MCAM	VEGF2	24	CD146
VEGFA		25	VEGF
E2F1	VEGFA, BMP4, CYR61, NUPR1, PLOD2, P4HA1, ADAMTS, LGALS3, ANGPT2	26	
E2F2	VEGFA, BMP4, CYR61, NUPR1, PLOD2, P4HA1, ADAMTS, LGALS3, ANGPT2	26	
E2F3	VEGFA, BMP4, CYR61, NUPR1, PLOD2, P4HA1, ADAMTS, LGALS3, ANGPT2	26	
GH		27	
EGFR		28	

**Note:**

The “primary gene” is the target of the stimulus. The “secondary genes” are genes that are also modified by the initial stimulus, therefore, could be also related with the pathogenesis.



**Table S2.** Identification of pathogenic genes. Gene polymorphism or mutation studies (Group 2)

GENE	ASSOCIATION [REFERENCE]
NAT2	+ <sup>29</sup> , - <sup>30</sup>
AGER	+ <sup>31</sup>
AHR	+ <sup>32</sup>
APEX1	+* <sup>33</sup>
FAS	+* <sup>34</sup> , +* <sup>35</sup>
FASLG	+* <sup>36</sup>
AR	+* <sup>37</sup>
ATM	+* <sup>38</sup> , +* <sup>39</sup>
BACH1	+* <sup>40</sup>
BARD1	+* <sup>39</sup>
CCND1	+* <sup>41</sup> , + <sup>42</sup> , +* <sup>43</sup>
BRCA1	+* <sup>44</sup>
BRCA2	+* <sup>44</sup> , + <sup>45</sup>
CASP8	+* <sup>39</sup> , +* <sup>46</sup>
CASP10	+ <sup>47</sup>
CAT	+ <sup>48</sup>
CDH1	+ <sup>49</sup>
CDKN1B	+ <sup>50</sup>
CHEK1	+ <sup>39</sup>
CCR5	+* <sup>51</sup> , - <sup>52</sup>
COMT	+* <sup>53</sup>
CYP1A1	+* <sup>54</sup> , - <sup>55</sup>
CYP1B1	+* <sup>56</sup>
CYP3A4	+* <sup>57</sup>
CYP19A1	+ <sup>39</sup>
NQO1	+* <sup>58</sup> , +* <sup>59</sup>
ERBB2	+* <sup>60</sup>
ERCC1	+* <sup>61</sup>
ERCC2	+* <sup>62</sup>
ESR1	+* <sup>63</sup> , +* <sup>64</sup> , +* <sup>65</sup>
ESR2	+ <sup>66</sup>
FGFR2	+* <sup>67</sup> , + <sup>68</sup>
FGFR4	+* <sup>69</sup>
VEGFD	+* <sup>70</sup>
XRCC6	+ <sup>71</sup>
GH1	+ <sup>72</sup>
GPX1	+* <sup>73</sup>
GSTM1	+* <sup>74</sup>
GSTP1	+* <sup>74</sup> , +* <sup>75</sup> , +* <sup>76</sup> , +* <sup>77</sup>
GSTT1	+* <sup>74</sup>
HIF1A	+* <sup>78</sup> , +* <sup>79</sup>

HRAS	+ <sup>80</sup>
ICAM1	+* <sup>81</sup>
IGF1	+ <sup>82</sup>
IGFBP3	+ <sup>83</sup>
IL1B	+ <sup>84</sup>
IL6	+ <sup>85</sup>
LEP	+* <sup>86</sup>
LEPR	+* <sup>87</sup>
LSP1	+* <sup>88</sup>
LTA	+* <sup>89</sup>
MDM2	+* <sup>90</sup> , +* <sup>91</sup> , +* <sup>92</sup>
MAP3K1	+* <sup>93</sup>
MMP1	+ <sup>94</sup>
MMP2	- <sup>95</sup> , +* <sup>96</sup>
MMP3	+ <sup>97</sup>
MMP9	+ <sup>98</sup>
MSH3	+* <sup>99</sup>
MTHFR	+* <sup>100</sup> , + <sup>101</sup>
NBN	+* <sup>39</sup>
NPAS2	+ <sup>102</sup>
OGG1	+ <sup>103</sup> , +* <sup>104</sup>
PGR	+* <sup>105</sup>
ABCB1	+ <sup>106</sup>
PIN1	+* <sup>107</sup>
PPARG	+ <sup>108</sup>
PTGS2	+ <sup>109</sup>
RAD51	+* <sup>110</sup> , + <sup>111</sup>
RAD51C	+ <sup>112</sup>
CXCL12	+ <sup>113</sup> , + <sup>114</sup>
SHBG	+* <sup>115</sup>
SIPA1	+ <sup>116</sup>
SOD2	+* <sup>117</sup>
AURKA	+* <sup>118</sup>
SULT1A1	+* <sup>119</sup> , +* <sup>120</sup> , + <sup>121</sup>
TCF7L2	+ <sup>122</sup>
TERT	+ <sup>123</sup>
TGFB1	+* <sup>124</sup>
TGFBR1	+* <sup>125</sup>
TNF	+* <sup>126</sup>
TP53	+ <sup>39</sup> , +* <sup>127</sup>
TYMS	+* <sup>128</sup>
VDR	+* <sup>129</sup>
VEGFA	+* <sup>130</sup>
VEGFC	+* <sup>130</sup>
WRN	+* <sup>131</sup>

XPC	+ <sup>132</sup>
XRCC1	+* <sup>133</sup> , +* <sup>134</sup> , +* <sup>135</sup>
XRCC2	+ <sup>136</sup>
XRCC3	+* <sup>137</sup> , + <sup>138</sup>
XRCC5	+ <sup>71</sup>
SLC4A7	+ <sup>139</sup>
HOXB13	+* <sup>140</sup>
SMC2	+ <sup>141</sup>
CHEK2	+* <sup>39</sup> , +* <sup>142</sup> , + <sup>143</sup>
TOX3	+* <sup>144</sup>
FOXP3	+* <sup>145</sup>
TLR9	+ <sup>146</sup>
UGT1A1	+* <sup>147</sup>
ZNF350	+* <sup>45</sup>
PALB2	+ <sup>148</sup>
BRIP1	+* <sup>40</sup>

**Note:**

Association: (+), (-) indicates that the study found at least one polymorphism with positive or null association, respectively. The (+\*) notation indicates that some polymorphisms were positive associated in at least one type of population.

**Table S3.** Identification of pathogenic genes. Final list matching G1 + G2.

<b>FINAL LIST (G1 + G2) (n = 145)</b>
ABCB1 (5243), AGER (177), AHR (196), AKT1 (207), APC (324), APEX1 (328), AR (367), ATM (472), ATXN1 (6310), AURKAIP1 (54998), BACH1 (571), BARD1 (580), BRCA1 (672), BRCA2 (675), BRIP1 (83990), CASP10 (843), CASP8 (841), CAT (847), CCND1 (595), CCNE1 (898), CCR5 (1234), CDH1 (999), CDK1 (983), CDKN1B (1027), CHEK1 (1111), CHEK2 (11200), COMT (1312), COX2 (4513), CXCL12 (6387), CYP19A1 (1588), CYP1A1 (1543), CYP1B1 (1545), CYP3A4 (1576), E2F1 (1869), E2F2 (1870), E2F3 (1871), EGFR (1956), ERBB2 (2064), ERBB3 (2065), ERCC1 (2067), ERCC2 (2068), ESR1 (2099), ESR2 (2100), FAS (355), FASLG (356), FGF1 (2246), FGF3 (2248), FGF7 (2252), FGF8 (2253), FGFR2 (2263), FGFR4 (2264), FOXP3 (50943), GH1 (2688), GJB2 (2706), GPX1 (2876), GSTM1 (2944), GSTP1 (2950), GSTT1 (2952), HGF (3082), HIF1A (3091), HOXB13 (10481), HRAS (3265), ICAM1 (3383), IGF1 (3479), IGF1R (3480), IGF2 (3481), IGFBP3 (3486), IL1B (3553), IL6 (3569), INT3 (65123), ITGB1 (3688), JAK2 (3717), KRAS (3845), LEP (3952), LEPR (3953), LPA (4018), LSP1 (4046), LTA (4049), MAP3K1 (4214), MCAM (4162), MDM2 (4193), MET (4233), MMP1 (4312), MMP2 (4313), MMP3 (4314), MMP9 (4318), MSF (10801), MSH3 (4437), MTHFR (4524), MYC (4609), NAT2 (10), NBN (4683), NOTCH4 (4855), NPAS2 (4862), NQO1 (1728), NRAS (4893), NRG1 (3084), OGG1 (4968), PALB2 (79728), PDK1 (5163), PGR (5241), PIN1 (5300), PPARG (5468), PTEN (5728), PTGS2 (5743), RAD51 (5888), RAD51C (5889), RB1 (5925), RET (5979), SHBG (6462), SIPA1 (6494), SLC4A7 (9497), SMARCA4 (6597), SMC2 (10592), SOD2 (6648), SRC (6714), STAT1 (6772), STAT5A (6776), SULT1A1 (6817), TCF7L2 (6934), TERT (7015), TFF1 (7031), TGFA (7039), TGFB1 (7040), TGFB1 (7040), TGFB1 (7040), TIMP3 (7078), TLR9 (54106), TNF (7124), TOX3 (27324), TP53 (7157), TYMS (7298), UGT1A1 (54658), VDR (7421), VEGFA (7422), VEGFC (7424), VEGFD (2277), WNT1 (7471), WRN (7486), XPC (7508), XRCC1 (7515), XRCC2 (7516), XRCC3 (7517), XRCC5 (7520), XRCC6 (2547), ZNF350 (59348).

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