1	
2	
3	Inherited defects in natural killer cells shape tumor immune
4	microenvironment, clinical outcome and immunotherapy response
5	
6	
7	Xue Xu <sup>1,+</sup> , Jianqiang Li <sup>2,+,*</sup> , Jinfeng Zou <sup>3,+</sup> , Xiaowen Feng <sup>1</sup> , Chao Zhang <sup>4</sup> , Ruiqing Zheng <sup>1</sup> , Weixiang
8	Duanmu <sup>4</sup> , Arnab Saha-Mandal <sup>1</sup> , Zhong Ming <sup>2</sup> , Edwin Wang <sup>1,5,*</sup>
9	
10	
11	1. University of Calgary, Cumming School of Medicine, Calgary, Alberta, Canada
12	2. School of Computing, Shenzhen University, Shenzhen, Chain
13	3. Princess Margaret Cancer Center, University Health Network, Toronto, Ontario, Canada
14	4. Department of Mathematics, Dalian Institute of Technology, Dalian, China
15	5. Department of Medicine, McGill University, Montreal, Canada
16	
17	
18	
19	Contact: EW (edwin.wang@ucalgary.ca)
20	
21	+ co-first authors
22	* corresponding authors
23	
24	
25	

#### 26 Abstract

27

28 Tumor immune microenvironment (TIME) plays an important role in metastasis and 29 immunotherapy. However, it has been not much known how to classify TIMEs and how TIMEs are 30 genetically regulated. Here we showed that tumors were classified into TIME-rich, -intermediate and -31 poor subtypes which had significant differences in clinical outcomes, abundances of tumor-infiltrating 32 lymphocytes (TILs), degree of key immune programs' activation, and immunotherapy response across 33 13 common cancer types (n = -6,000). Furthermore, TIME-intermediate/-poor patients had significantly 34 more inherited genetic defects (i.e., functional germline variants) in natural killer (NK) cells, antigen 35 processing and presentation (APP) and Wnt signaling pathways than TIME-rich patients, and so did 36 cancer patients than non-cancer individuals (n=4,500). These results suggested that individuals who 37 had more inherited defects in NK cells, APP and Wnt pathways had higher risk of developing 38 cancers. Moreover, in the 13 common cancers the number of inheritably defected genes of NK 39 cells was significantly negative-correlated with patients' survival, TILs' abundance in TIMEs and 40 immunotherapy response, suggesting that inherited defects in NK cells alone were sufficient to shape 41 TILs' recruitment, clinical outcome and immunotherapy response, highlighting that NK cell activation 42 was required in the 13 cancer types to drive the recruitment of immune troops into TIMEs. Thus, we 43 proposed that cancer was a disease of NK cell inherited deficiencies. These results had implications in 44 identifying of high-risk individuals based on germline genomes, implementing precision cancer 45 prevention by adoptive transfer of healthy NK cells, and improving existing immunotherapies by 46 combining of adoptive NK cell transfer (i.e., converting TIME-intermediate/-poor tumors into TIME-47 rich tumors) in and anti-PD-1 or CAR-T therapy.

48

#### 50 Introduction

51 In the past two decades, classification of tumors based on omic data has resulted distinct tumor 52 molecular subtypes for each cancer type and then provided a framework to study the molecular 53 mechanisms such as oncogenic pathways and discover drug targets for tumors. Moreover, tumor 54 molecular subtypes enable to inform clinical outcomes and treatments. For example, treatment options can be made based on either Her2+, luminal or basal subtypes of breast cancer (1, 2, 3, 4). However, an 55 56 enormous complexity of cancer subtypes, tumor microenvironment, subclones and somatic genomic 57 alteration landscapes has been reported. For example, tumor molecular subtypes and patient 58 stratifications based on tumor gene expression profiles showed that each cancer type has its own 59 subtypes which were often unique and not commonly shared between any 2 cancer types. Each subtype 60 has its own oncogenic pathways and somatic mutating drivers.

Tumor microenvironments often interact with tumor cells to affect metastasis and clinical outcomes. In 61 62 the past few years, immune-checkpoint therapy (ICT) has been able to successfully eliminate tumors 63 in 10-40% of patients with melanoma and other cancer types, however, in the majority of patients, 64 ICT failed to have their intended effect (<sup>5, 6</sup>). It has been believed that understanding of tumor 65 infiltrated immune cells (TILs) in tumor immune microenvironment (TIME) could help in getting 66 insights into ICT response, resistance and might improve existing immunotherapies (<sup>7, 8</sup>). Infiltrating 67 T cells are a critical component for ICT response. However, recently it has been shown that NK 68 (natural killer) cell activation is required in melanoma to recruit CD103+ DC (dendritic cell) and then 69 CD8+ effector T cells. Except the TIL-T cell recruitment function, the best-known role of NK cells is 70 cancer cell killing and tumor immunosurveillance. To fulfil this function, distinct from T and B cells, 71 NK cell is not mediated by antigen specificity but through multiple germline-encoded activating and inhibiting receptors (9, 10, 11), the complex balance of inhibitory and activating signals promotes self-72 73 tolerance or drives potent effector function of NK cells.

Historically, tumor molecular subtypes have generated lots of insights into the underlying molecular mechanisms of tumorigenesis, metastasis and informing of treatments. With advances of cancer ICT, CAR-T and other immunotherapies, it has a strong interest in stratifying TIMEs into TIME subtypes. Further stratification of patients on the basis of their TIMEs could discover better insight into overall survival and underlying molecular mechanisms for ICT response and help identify new immunotherapeutic targets. However, so far, we have no idea how to study TIMEs and lack of efficient tools to classify TIMEs. Here we conducted an analysis of the omic data (i.e., tumor RNA-seq and

- 81 whole-exome sequences of germline genomes) of TCGA (The Cancer Genome Atlas) cancer patients
- 82 (n=-6,000) representing 13 common cancer types, and a non-cancer cohort (n=4,500) to show that
- tumors were classified into three universally distinct TIME subtypes across the 13 common cancer
- 84 types. They were different in prognosis, TILs' abundance and degree of immune programs' activation,
- 85 regardless of cancer type. Inherited defects of NK cells, antigen processing and presentation (APP) and
- 86 Wnt pathways in patients' germline genomes modulated TIME subtypes and ICT response.
- 87 Importantly, we showed that inherited defects in NK cells alone were sufficient to regulate TILs'
- 88 abundance in TIMEs, clinical outcomes and immunotherapy response. Further, individuals who have
- 89 inherited defects in NK cells, APP and Wnt pathways bear high-risk of developing cancers.

### 90 **Results**

# 91 Three universal TIME subtypes across 13 common cancers

92 To classify tumors into TIME subtypes, we applied the unsupervised clustering of gene expression 93 data (i.e., melanoma data from TCGA) based on a set of genome-wide CRISPR-Cas9 screen-94 determined essential genes (i.e., ICT essential genes, n=1,294) from a previous study (<sup>12</sup>) and other known tumor immune related genes  $(^{13, 14})$  (see Methods). We found that melanoma tumors were 95 96 classified into three TIME subtypes (Fig 1a). Similarly, the three TIME subtypes were repeatedly 97 obtained in the 13 common cancer types (Supplementary Fig 1): bladder urothelial carcinoma (BLCA), 98 breast invasive carcinoma (BRCA), cervical squamous cell carcinoma and endocervical 99 adenocarcinoma (CESC), colon adenocarcinoma (COAD), head and neck squamous cell carcinoma 100 (HNSC), kidney renal clear cell carcinoma (KIRC), lower grade glioma (LGG), lung adenocarcinoma 101 (LUAD), lung squamous cell carcinoma (LUSC), pancreatic adenocarcinoma (PRAD), skin cutaneous 102 Melanoma (SKCM), stomach adenocarcinoma (STAD), thyroid carcinoma (THCA) and uterine corpus 103 endometrial carcinoma (UCEC). These results suggested that TIME subtypes were much simpler than 104 tumor molecular subtypes, each of which was unique and couldn't be shared by any two cancer types. 105 Thus, the universal TIME subtypes provided a means to identify subtypes' unifying features and to 106 understand the underlying common molecular mechanisms of each TIME subtype. 107

- 108 To discover the common features and critical differences which defined the 3 distinct TIME subtypes,
- 109 we compared their gene expression profiles, TILs' abundance in TIMEs and clinical outcomes. The
- abundance of TILs in TIMEs were significantly decreased from TIME-rich ('immune-hot' tumors), -
- 111 intermediate ('immune-cold' tumors) to TIME-poor subtype ('immune-desert' tumors) (Fig 1b,
- 112 Supplementary Table 1). It has been known that TILs are associated with tumor prognosis, thus we

113 hypothesized that clinical outcomes could be different between TIME subtypes. In fact, both TIME-114 poor and -intermediate tumors had significantly poorer clinical outcomes than TIME-rich tumors (Fig 115 1c), however, patient survival differences were not significant between TIME-poor and -intermediate 116 tumors. Pathway enrichment analysis of the significantly modulated genes between subtypes showed 117 that the degree of the activated (i.e., represented by gene expression of each pathway or program) 118 immune programs such as APP, NK cell-mediated cytotoxicity, T cell receptor singling pathways were 119 significantly decreased from TIME-rich, -intermediate to -poor subtype (Fig 1d and Supplementary Fig 120 2). These results suggested that TIME-poor and -intermediate tumors had lower degree of activated 121 immune programs, so that they could had better chance to escape immunosurveillance. For example, 122 APP is an immunological process that prepares and presents antigens to T cells. NK effector and T cell 123 receptor signaling pathways function as tumor cell killing. Therefore, lower activity of APP, NK cells 124 and T cell receptor singling allows tumor cells to having fewer immune constraints. These results were 125 repeatedly observed across the 13 common cancer types, suggesting that the TIME subtypes are not 126 only universal subtypes across cancer types but also share common cellular and clinical features.

127

In general, TIME-rich, -intermediate and -poor tumors represent 25.35%, 32.94%, and 41.70% of the tumors, respectively, depending on cancer types (Supplementary Table 2). These results indicated that TIME-rich patients represent only a small fraction of tumors, and more than 70% of the tumors are either TIME-poor, or -intermediate tumors, most of which are known to non-respond to ICT. These results explain why only 10-40% of tumors (i.e., depending on cancer type) respond to ICT.

#### 133 Inherited defects in NK cells shape TIME subtypes and clinical outcomes

134 The discovery of the universal TIME subtypes across the 13 common cancer types triggered us to 135 hypothesize that the TIME subtypes could be modulated by common genetic regulators. We previously 136 proposed that pre-existing inherited variants in germline genomes of cancer patients could play an 137 important role in shaping somatic mutations, CNVs and oncogenic pathways in their paired tumor 138 genomes (<sup>15</sup>). Furthermore, we have shown that inheritably functional variants of breast cancer patients significantly predicted tumor recurrence  $\binom{16, 17}{1}$ , and the risk for breast, brain and other cancers  $\binom{18}{1}$ . 139 140 Moreover, inheritably functional variants of patients could be used to predict key somatic-mutated 141 genes in their paired tumor genomes (Zaman et al., unpublished data). Finally, cancer patients' 142 germline genomes contain specific genomic patterns which are associated with cancer risk and clinical 143 outcomes (Feng et al., unpublished data). These results raised a question whether cancer patients' 144 germline genomes modulated TIME subtypes.

145 To answer this question, we compared the functional germline variants (termed as inherited defects here, see Methods) of the patients between TIME subtypes and showed that genetic makeups of the 146 147 patients were significantly different between them (Supplementary Fig 3): TIME-poor/-intermediate 148 and TIME-rich patients had significantly differentially inherited genetic defects. Further pathway 149 enrichment analysis showed that more than 30% of the defected or modulated pathways were 150 associated with NK cell deficient phenotypes, NK cell associated virus infections, and the NK cell-151 mediated cytotoxicity pathway (Fig 2a, Supplementary Fig 4). For example, among the significantly 152 differential pathways and phenotypes, 7 of them were known NKD (NK cell deficiency) phenotypes (<sup>19, 20, 21</sup>) such as Epstein-Barr virus (EBV) infection, Herpes simplex infection, Leishmaniasis, 153 154 Rheumatoid arthritis, Type I diabetes mellitus, long-term depression and viral myocarditis, while 7 of 155 them were NK cell-related virus infections such as Graft-versus-host disease, HTLV-I infection, 156 Hepatitis B and C, Influenza A, Asthma and IBD (Fig 1d, 2a and 2b). These results strongly suggested 157 that TIME-poor/-intermediate patients might have more inherited defects in their NK cells than TIME-158 rich patients.

159

160 NK cells are the 'first-line immune cells' which enable to guickly detect and attack tumor cells and 161 viruses. NK cells are able to control tumorigenesis by accurately regulating the distinct germline 162 encoded inhibitory and activating NK cell surface receptors. In general, an excess of activating over inhibitory signals triggers the production and release of effector molecules, which can lead to the death 163 of the infected or transformed cancer cell (22). Thus, to further explore the association between NK cell 164 inherited defects with cancer progression and metastasis, we compiled a comprehensive set of NK cell 165 166 genes including NK cell receptors and ligands, genes in NK cell signaling pathways (i.e., KEGG NK cell-mediated cytotoxicity pathway (<sup>23, 24, 25</sup>), and then conducted Fisher's tests to identify genes which 167 168 had significantly differential frequencies between TIME-rich group and TIME-poor/-intermediate 169 group. For a given cancer type, we found 15-20 defected NK cell genes which had significantly higher 170 frequencies in TIME-poor/-intermediate group than TIME-rich group (FDR-corrected p <0.25). The 171 gene list for each cancer type was different, which could be associated with the diversity of tissue-172 resident NK cells, although many of the significantly defected NK cell genes of the 13 cancer types 173 were shared. In total there were 103 such genes (i.e., termed as NK-genes here), 70 of which appeared 174 in at least two cancer types. Among the 70 NK-genes, 37.2%, 25.8%, 24.3%, and 12.7% are known NKD genes (19, 20, 21), NK cell receptors and ligands, NK cell singling genes but also expressed in cell 175 176 signaling in T or other immune cells (i.e., mainly innate immune cells, termed as 'global immune cell

177 genes' here) and universal genes (i.e., expressed in many cell types), respectively (Supplementary

- 178 Tables 3 and 4).
- 179

180 We further asked if inherited defected NK-genes were correlated with clinical outcomes. To answer 181 this question, for each cancer type, we top-to-bottom ranked the patients based on the number of 182 inheritably defected NK-genes. We defined top 40% and bottom 40% of the ranked patients as high-183 and low-NK cell defected groups, respectively, to conduct survival analysis. In 10 of the 12 cancer 184 types (i.e., no survival data were available for THCA) except LGG and KIRC, the high-NK cell 185 defected group had significantly shorter survival than the low-NK cell defected group (Fig 3a). 186 Similar results were obtained when using top 30% and bottom 30% of the ranked patients as high-187 and low-NK cell defected groups, respectively. These results suggested that NK cells inherited 188 defects could play an important role in tumor recurrence and overall survival in most of the cancer 189 types. Given the fact that TILs' abundance was different between TIMEs, we hypothesized that NK 190 cell defected gene number could be negatively correlated with the TILs' abundance in TIMEs. 191 Indeed, it was true that for all the 13 cancer types (Fig 3b, Supplementary Fig 5), the abundance of 192 immune cell troops such as NK, NKT, CD103+ DC (cDC), activated CD8+ T, CD4+ T, activated B, all 193 kinds of T cells and 23 other types of immune cells were negatively correlated with the defected gene 194 number in NK cells, suggesting that NK cells could be an important factor recruiting other immune 195 cells into TIMEs.

196

197 NKD genes and NK cell receptors/ligands are more preferentially involved in either NK cell-mediated 198 cytotoxicity, NK cell development or proliferation (<sup>11, 26</sup>), while the global immune cell genes could 199 influence the immune response of not only NK cells but also other immune cells. On the other hand, 200 the universal genes play important roles in cell signaling of not only NK cells but also other cell types 201 including tumor cells. Therefore, NKD genes and NK receptors/ligands are more NK cell-specific (i.e., 202 representing 63% of the NK-genes, termed as NK-specific-genes here), while the global immune cell 203 genes (i.e., representing 24.3% of the NK-genes) and the universal genes (i.e., representing 12.7% of 204 the NK-genes) are expressed in multiple immune cells and non-immune cell types, respectively. Thus, 205 we raised a question whether the correlations observed in Fig 3a, 3b and Supplementary Fig 5 were 206 truly from NK cell defected genes. By extending the same analyses in Fig 3a and 3b using only the 207 universal genes, there were not any correlation as shown in Fig 3a and 3b, suggesting that inherited 208 defects in the universal genes alone are insufficient to modulate either TILs in TIMEs or clinical 209 outcomes. Next, we re-did the same analyses by combining of the universal genes and the global

immune cell genes (i.e., representing 37% of the NK-genes, termed as NK-immune-universal-genes
here) and the NK-specific-genes, respectively. For the NK-immune-universal-genes, correlations as

- shown in Fig 3a (i.e., survival) were not observed, on the other hand, for the NK-specific-genes, such
- 213 correlations were reproduced across the 10 cancer types. These results suggested that the NK-specific-
  - 214 genes are sufficient to shape clinical outcomes, but the NK-immune-universal-genes were not.
  - 215

216 Similarly, significantly negative correlations between TILs' abundance in TIMEs and the number of 217 the inheritably defected NK-specific-genes were reproduced in 10 cancer types including BLCA, 218 BRCA, KIRC, LAUD, LUSC, THCA, UCEC, HNSC, LGG, and SKCM (Fig 3b, Supplementary Fig 219 5). In particular, the correlations derived from the NK-specific-genes were much stronger than those 220 derived from the NK-genes in 7 cancer types (i.e., BLCA, BRCA, KIRC, LAUD, LUSC, THCA and 221 UCEC, Fig 3b, Supplementary Fig 5). On the other hand, weaker negative correlations (i.e., correlation 222 co-efficiencies were 2-10 times less than those derived from the NK-genes) and weaker statistical 223 significances (i.e., p values in the range of 0.01-0.05) were observed for some immune cells in some 224 cancer types when using the NK-immune-universal-genes (Fig 3b, Supplementary Fig 5). These results 225 suggested that inherited defects of the NK-specific-genes are sufficient to impair communications 226 between NK cells and other immune cells and then block TILs' recruitment into TIMEs. Of note, in 227 COAD, STAD, and PRAD, both NK-specific-genes and NK-immune-universal-genes did not 228 reproduce the negative correlation (i.e., for TILs in TIMEs) derived from the NK-genes. PRAD has 229 dense stroma (<sup>27</sup>) which could need the whole NK gene set (i.e., NK-genes) for TILs' recruitment. NK 230 cells surrounding both COAD and STAD are directly interacting with environmental factors such as 231 microbiome, food, drinks and others so that NK cells associated with both COAD (colon cancer) and STAD (gastric cancer) are much more complex. These data highlighted that inherited defected in NK 232 233 cells are one of the key genetic factors in shaping TIME subtypes, TILs' abundances and clinical 234 outcomes.

235

Based on these insights, we hypothesized that NK cell was a critical factor for recruiting immune
troops into TIMEs. This hypothesis is partially supported by two recent studies which had no idea
about NK cell inherited defects (<sup>27, 28</sup>), but showing that depletion of NK cells resulted in failed
recruitment of CD8+ T cells to the tumor microenvironment in melanoma mice. They further showed
that NK cells recruited CD103+ DC, which in turn were required for the recruitment of effector T
cells. Our results here suggested that NK cells could be able to recruit not only CD103+ DC (cDC) and
CD8+ T cells but also 30 other immune cells. Because NK cells act as first responders to detect and

kill cancer cells, it is reasonable to believe that NK cells could sequentially recruit many other
immune cells including CD103+ DC and T cells into the tumor microenvironment. Thus, NK cells
could recruit a whole immune troop but not only one or two immune cell types into TIMEs.

246

This insight provides a potential opportunity that adoptive cell transfer of NK cells from healthy donors 247 248 could convert a TIME-poor tumor into a TIME-rich tumor. Adoptive NK cell was safe and does not 249 cause a graft-versus-host disease attack on the recipients. Thus, we hypothesized that adoptive NK cell 250 transfer of healthy donors (i.e., allogeneic) to a patient could have better clinical outcomes than 251 adoptive transfer of NK cells from the patients themselves (i.e., allogeneic), because cancer patients' 252 own NK cells are defected and don't function very effectively. This hypothesis is supported by a recent 253 clinical trial showing that allogenic adoptive NK cell transfer was much better than autogenic NK cell immunotherapy for breast cancer outcomes (<sup>29</sup>). TIME-rich tumors are more suitable to conduct 254 255 immunotherapy than TIME-poor tumors, while TIME-rich tumors can gain significantly more survival 256 benefit than TIME-poor tumors for neoadjuvant chemotherapy as well. For example, a meta-analysis of 257 13 studies showed that higher abundance of TILs in pre-treatment tumor biopsy was correlated with better pathological complete response rates to neoadjuvant chemotherapy(<sup>30, 31, 32, 33, 34</sup>). Therefore, it is 258 259 a great interest to improve patient outcomes by applying adoptive transfer of healthy, functional NK 260 cells to convert TIME-poor tumors into TIME-rich tumors which could be in turn treated with 261 chemotherapy or immunotherapy. A recent clinical trial partially supported this hypothesis: adoptive 262 transfer of NK cells in combination with chemotherapy in stage IV colon cancers significantly 263 prevented recurrence and prolonged survival than chemotherapy alone. Most importantly, they found 264 that poorly differentiated colon cancers were more susceptible to adoptive NK cell transfer than well-265 differentiated ones (<sup>35</sup>). Poorly and well differentiated cancers are shorter and longer survival patients, 266 respectively, which are corresponding to TIME-rich and -poor tumors, respectively. Therefore, these 267 results agree with our above hypothesis. Another study also supported this hypothesis: the combination therapy of anti-PD-1 antibodies and activated autologous NK cells significantly delayed tumor 268 269 progression in glioma-bearing animals as compared to the monotherapy regimens of anti-PD-1 or 270 stimulated NK cells alone  $(P < 0.001)(^{36})$ .

271

#### 272 Tumorigenesis and metastasis are not random events and cancer patients are highly selected

273 As shown in Fig 2a and Supplementary Fig 4, except NK cell inherited defects, TIME-poor/-

274 intermediate patients had significantly more defected APP and Wnt pathway genes than TIME-rich

275 patients. APP is a biological process which presents antigens to T cells, functional defects in APP could

276 lead tumor cells to escape T cell surveillance. However, careful analyses showed that APP pathway 277 genetic defects were not significantly associated with clinical outcomes and TILs' abundance. These 278 results suggested that APP pathway defects alone were not sufficient to shape either clinical outcomes 279 or TIME subtypes. In addition, it has been shown that activated Wnt signaling pathway in tumors 280 excluded the recruitment of T cells into TIMEs (<sup>37</sup>). Furthermore, somatic mutations of the Wnt 281 pathway in tumors could activate the pathway to prevent T cells to be recruited into TIMEs  $(^{38})$ . Here 282 we showed that in most of the cancer types the number of inherited defects in Wnt pathway in germline 283 genomes had a positive correlation with the gene expression of the Wnt pathway (i.e., pathway 284 activation) in their paired tumors, suggesting that a positive correlation between inherited defects in the Wnt pathway and activation of the pathway, which is similar to the somatic mutations in genes of the 285 286 pathway.

287

288 The number of the inheritably defected genes in the Wnt pathway had weakly negative correlations 289 (i.e., with marginally significant p values in the range of 0.02-0.05) with clinical outcomes in 8 cancer 290 types (i.e., BLCA, BCRA, HNSC, LAUD, LUSC, PRAD, STAD and UCEC) and no such correlation 291 with other cancer types (Supplementary Fig 6). Similarly, Wnt pathway inheritably defected gene 292 number had negative correlations with the abundance of TILs in TIMEs (Supplementary Fig 7) in eight 293 cancer types (i.e., HNSC, KIRC, LGG, LUAD, LUSC, SKCM, STAD and THCA), however, the 294 correlations were weaker (i.e., in terms of correlation co-efficiencies and correlation significance 295 represented by p values) than those derived from NK cells. These results suggested that inheritably 296 defected in Wnt pathway could shape TILs' recruitment in some cancer types, and the influences were 297 much weaker than NK cells. Next, we asked if inheritably defects of the Wnt pathway and NK cells 298 worked in a synergy manner. To answer this question, we conducted the correlation analysis using the 299 genes combined from the NK cells and the Wnt pathway and showed that negative correlations 300 between the inheritably defected gene number and the TILs' abundance in TIMEs remained in eight 301 cancers but much weaker than the correlations derived from either NK cells or Wnt pathway alone. 302 These results suggested that both NK cells and Wnt pathway were parallel and complementary 303 modulators to shape TILs recruitment, implying that to reverse immune exclusion in TIMEs, Wht 304 signaling inhibitors could be better than adoptive NK cell transfer in some tumors but not most of the 305 tumors.

306

307 Together with the discovery that TIME-rich tumors have significantly longer survival than TIME-308 poor/-intermediate patients, we concluded that inherited defects in NK cells and Wnt pathways were

309 associated with metastasis and clinical outcomes. These results highlighted that metastasis is affected 310 by inherited defects and is not a random process. Similarly, significantly more inherited defects in NK 311 cells, APP and Wnt pathways were observed between non-cancer individuals and cancer patients in the 312 13 common cancer types (Supplementary Fig 8). They were even more significant between TIME-313 poor/-intermediate patients and non-cancer individuals (Fig 2b and Supplementary Fig 9). These results 314 suggested that individuals who bear inherited defects in NK cells, APP and Wnt pathways have higher 315 risk to get cancer. This hypothesis is indirectly supported by a study showing that individuals with 316 lower NK cytotoxic activity in peripheral blood had a higher incidence of cancer (n=3,500 with 11-year 317 follow-up)<sup>39</sup>). Similarly, previous studies showed that impaired NK cell activity was found in family members of patients with different types of cancer (<sup>40, 41, 42</sup>). Importantly, such inherited defects in NK 318 319 cells, APP and Wnt pathways were repeatedly observed between non-cancer and cancer individuals 320 (Fig 2b, Supplementary Fig 9), between TIME-rich and TIME-intermediate/-poor patients (Fig 2a, 321 Supplementary Fig 4, Fig 1d), suggesting that these individuals were highly selected for tumorigenesis 322 and metastasis. The immune programs (defects in NK cells, APP and Wnt pathways) are carried from 323 germline genomes to their paired tumors. In fact, the number of inherited defects in the NK cells, APP 324 and Wnt pathways was gradually increased from non-cancer cohort, TIME-rich, -intermediate to -poor 325 subtypes, suggesting that inherited defects in the NK cells, APP and Wnt pathways have a profound 326 impact on cancer risk, TIME subtypes and clinical outcomes. These insights provided a potential 327 opportunity to identify high-risk cancer subpopulation based on the inherited defects in NK cells, APP 328 and Wnt pathways, further, adoptive NK cell transfer from healthy donors to high-risk individuals 329 could postpone or prevent cancer development. This hypothesis is partially supported by a study 330 showing that NK cell depletion in melanoma mice resulted in substantial metastasis, but adoptive 331 transfer of NK cells protects NK cell-deficient mice from tumor establishment (<sup>43</sup>).

332

333 In addition, as shown in Fig 2b, Type I diabetes and long-term depression phenotypes were linked to 334 some cancers, suggesting that they were genetic diseases as well. Diabetes and obesity have been 335 shown to be a risk factor for some cancers, for example, a meta-analysis of 121 cohorts including 20 336 million individuals and one million events confirmed that diabetes is a risk factor for all-site cancer (<sup>44</sup>), while obesity can increase cancer incidences of 13 cancer types (<sup>45</sup>). A 24-year follow-up study 337 showed that depression increases the risk of cancer (<sup>46</sup>), Moreover, a meta-analysis of 16 studies 338 (n=163,000) showed that cancer patients with anxiety and depression had a greater risk of dying from 339 340 all types of cancer (<sup>47</sup>). Impairing of the NK cell function is one of the common factors behind these 341 links. For example, obesity has been known to impair NK cell function and then lead to an increased

risk for severe infections and several cancer types ( $^{48, 49}$ ), while chronic family stress is consistently

343 associated with decreases in NK cell cytotoxicity (<sup>50</sup>). These results indicated that NK function

impaired by either genetic defects or regulatory factors such as depression, obesity and diabetes could

345 increase cancer incidence.

346

# 347 TIME subtypes could guide in immunotherapies

348 As shown above, both NK cell-mediated cytotoxicity and Wnt signaling pathways became the 349 hallmarks which enabled to significantly distinguish TIME-rich and TIME-intermediate/-poor subtypes. From the ICT clinical trials (<sup>51,52</sup>), we obtained 49 melanoma (SKCM, 10 responders) and 47 350 351 gastric (STAD, 12 responders) samples which had tumor RNA-seq data before administrating of ICT. We used the significantly modulated genes of both pathways between TIME subtypes to assign the 352 353 ICT-clinical trial samples into either TIME-rich or TIME-intermediate/-poor group based on the k-354 nearest neighbor algorithm (KNN, see Methods). By doing so, 70% and 30% of the ICT-responding 355 melanoma were assigned into TIME-rich and TIME-intermediate/-poor group, respectively. In contrast, 356 56% and 44% of the ICT non-responding melanoma were assigned into TIME-rich and TIME-357 intermediate/-poor group, respectively. Similarly, 58% and 42% of the ICT-responding gastric tumors 358 were assigned into TIME-rich and TIME-intermediate/-poor group, respectively. In contrast, 31% and 359 69% of the ICT non-responding gastric tumors were assigned into TIME-rich and TIME-intermediate/-360 poor group, respectively. Not surprisingly, these results indicated that TIME-rich patients were 361 enriched with ICT responders. Pathway enrichment analysis of tumor gene expression profiles showed 362 that TIME-rich non-responders had significantly higher gene expression in Wnt pathway (FDRcorrected  $p=5.3 \times 10^{-12}$  and  $4.0 \times 10^{-5}$  for melanoma and gastric tumors, respectively) than TIME-rich 363 364 non-responders, suggesting that using of Wnt inhibitors could improve ICT treatment for TIME-rich 365 non-responders. Similarly, genes of the NK cell-mediated cytotoxicity pathway (FDR-corrected p=2.5x10<sup>-3</sup> and 2.7x10<sup>-3</sup> for melanoma and gastric tumors, respectively) and APP (FDR-corrected 366 p=7.1x10<sup>-4</sup> for melanoma) were significantly lower expressed in TIME-intermediate/-poor non-367 responders than TIME-intermediate/-poor responders, suggesting that adoptive NK cell transfer in 368 369 combination with CAR-T or ICT could improve the existing immunotherapies for TIME-intermediate/-370 poor non-responders. However, it should be cautious about these conclusions due to the small number 371 of the clinical trial samples (n=96) here, more samples are needed to further validate these discoveries 372 in the future.

- 373
- 374

#### 375 Discussion

#### 376 A unified view of the tumor immune microenvironment

377 Tumor molecular subtypes could inform not only prognosis but also treatment. Here we showed that 378 TIMEs can be classified into three universal subtypes across 13 common cancer types. Different from 379 previous observations of the complex tumor molecular subtypes, each of which often has its own 380 unique features, the universal TIME subtypes were commonly shared by multiple cancer types, 381 providing a framework to get better insight into the unifying features of each TIME subtype and the 382 differences between the distinct TIME subtypes, and then understand why some tumors respond to 383 immunotherapy and some don't. Furthermore, this framework allows exploring genetic factors to 384 regulate TIMEs and could help in identifying new druggable targets. Regardless of cancer types, TIME 385 subtypes have unifying features: (1) TIME-rich patients have significantly longer survival than other 386 TIME subtypes, because (2) the abundance of the TILs in TIME-rich, -intermediate and -poor tumors is 387 gradually decreased. These features recaptured the known immune-hot, -cold and -desert tumors described previously based on immunohistochemistry (<sup>53, 54</sup>). It has been well-known that a lower 388 389 abundance of TILs in TIMEs is associated with more cancer recurrence and shorter survival (55, 56). (3) 390 signaling pathways associated with key immune programs such as APP, NK, and T cell signaling were 391 more highly activated in TIME-rich tumors than TIME-intermediate/-poor tumors. The degree of the 392 activated immune programs (i.e., represented by the expression levels of the pathway genes) was 393 gradually decreased from TIME-rich, -intermediate to -poor tumors. Lower level expression of the 394 genes in these immune-programs and pathways will allow tumors to escaping from immune attack. (4) 395 finally, ICT-responders were more enriched in TIME-rich tumors.

396

#### 397 Cancer is a NK cell deficient disease

398 The hypothesis of cancer immunosurveillance suggests that tumor cell transformation occurs 399 frequently, but is under constant control by the immune system. The immune system is able to identify 400 transformed cells that have escaped cell-intrinsic tumor-suppressor mechanisms and eliminate them before they can establish malignancy (<sup>57</sup>). Thus, if the individuals are genetically immunodeficient, 401 402 they could have a markedly increased incidence of cancer. In general, NK cells have a large repertoire 403 of germline-encoded inhibitory and activating receptors to sense 'danger' in the cell surfaces. The 404 germline-encoded receptors which recognize ligands associated with viral infection or cancer cell 405 transformation (<sup>10</sup>). Genetic defects in NK-genes including NK cell receptors and NKDs could impair NK cell functions. By conducting a unbiased scanning of germline genomes of cancer patients, we 406 407 provided a clearer view of the spectrum of malignancies associated with impaired NK cells and showed 408 that inherited defects affecting NK cell functions were sufficient to accomplish cancer

409 immunosurveillance of the immune system.

410

Among highly related pathways (i.e., NK cells, APP and Wnt pathways) examined, only NK-genes' 411 412 defects were correlated with both survival and the abundance of TILs in TIMEs. Most importantly, in 10 out of the 12 common cancers (i.e., no survival data were available for THCA), defects of the NK-413 414 specific-genes (i.e., NKDs + NK cell receptors) alone were sufficient to establish these correlations 415 (i.e., survival and TILs' abundance). Traditionally, the hypothesis of cancer immunosurveillance mainly focuses on T cell or other immune cells for their cell-killing function. Here we demonstrated 416 417 that to implement cancer immunosurveillance, NK cells could play a critical role in communicating 418 with many immune cells to recruit the whole immune troops into the cancer-transformed cell or 419 TIMEs. Specifically, our results suggested that NK cells could have two functions for controlling tumor 420 progression and metastasis: (1) cancer cell killing (2) recruiting immune troops into TIMEs. Here we 421 proposed a working model for NK cell-based immunosurveillance: NK cells are the first to arrive in the 422 tumor microenvironment and recruit CD103+ DC through the secretion of chemokines. TIL-DCs then 423 recruit effector T cells. Activated NK cells produce numerous cytokines, communicate with other 30 424 immune cells, and then recruiting the immune troops into the cancer cell or TIMEs. Anti-tumor 425 and anti-metastasis activity (i.e., survival differences between TIME subtypes) is thus the result of the 426 collaboration of distinct innate and adaptive immune cell types. Thus, inheritably defected NK-genes 427 could impair NK cell function and then block to recruit the immune troops to the cancer cell or into 428 TIMEs to conduct anti-tumor activity. Thus, we proposed that cancer is largely a disease of NK cell 429 deficiencies. This working model unraveled the cellular and molecular determinants (i.e., NK cells) of multiple immune cell recruitment to and retention in solid tumors' TIMEs. Thus, allogeneic adoptive 430 431 NK cell therapy (i.e., collecting healthy NK cells which have no inherited defects from donors and 432 infusing them into the patient) could convert immunotherapy-resistant, TIME-poor tumors into ICT/CAR-T-sensitive, TIME-rich tumors. This NK cell therapy could be a universal approach which is 433 434 independent of cancer types. Given the fact that more than 70% of the cancer patients are immune-cold 435 and -desert subtypes, successfully validating of this hypothesis will be a crucial step toward improving 436 the existing immunotherapies.

437

In addition, our results suggested that inherited defects in NK cells, APP and Wnt pathways were
positively selected in tumorigenesis and metastasis. Therefore, cancer patients are highly selected, and
thus, it provides an explanation for the fact that only 12-20% of the heavy smokers develop lung cancer

in their lifetime, although 85% of the lung cancer patients are heavy smokers (<sup>58, 59</sup>). Cancer causally
environmental factors play an important role in tumorigenesis, however, without a susceptible germline
genome (i.e., genetic defects in NK cells, APP and Wnt pathways), they still cannot induce cancer. We
proposed that germline genome is the most important factor in determining if a person will get cancer
in one's lifetime, and cancer is the result of the interactions between high-risk germline genomes and
risk-factors (i.e., environmental factors and lifestyles).

Thus, the discoveries in this study could open a new window to explore NK cell biology and lead to 447 448 novel thinking about identifying of high-risk individuals for early cancer detection, precision cancer 449 prevention and immunotherapy. Strategies to harness and augment NK cells for cancer therapy are a 450 relatively new and rapidly developing field and have not been used for cancer prevention yet. The 451 concept that cancer is a NK cell deficient disease could lead this field to new directions: (1) identifying 452 of high-risk population based on NK cell, APP and Wnt pathways' inherited defects, so that early 453 cancer detection or precision prevention (i.e., by avoiding in exposure in smoking, UV lights and other 454 risk factors) could be implemented. (2) Preventing or postponing of cancer development for the high-455 risk population by adoptive NK cell transfer. (3) Converting TIME-poor/-intermediate tumors into 456 TIME-rich tumors by manipulating NK cells, adoptive NK cell transfer or using Wnt signaling 457 inhibitors so that ICT or CAR-T therapy could be applicable. Finally, many open questions still 458 remained, for example, defected genes in NK cells were largely shared by different cancer types, 459 however, each cancer type has some unique NK cell gene defects. Given the fact that tissue/organ-460 resident NK cells are different and diverse (<sup>60</sup>), additional studies will be needed to elucidate if defected genes are dominantly expressed in tissue/organ-resident NK cells. If so, adoptive transfer of tissue-461 462 resident NK cells could be considered to be more efficient in cancer prevention and TIL's recruitments. 463 NK cells share lots of expression programs with NKT cells, which is a subset of innate-like T cells. 464 Both NK cells and NKT cells are cytotoxic cells, which trigger innate immune responses, provide the 465 first level of defense against infected cells and tumor cells, produce cytokines and trigger immune 466 responses without a prior sensitization by the immune system. Along this long, we suspected that the 467 inherited defects in NKT cells could also play similar roles which were discussed in this study, 468 although the cell number of the NK cells is nearly 200 times of the NKT cells.

469

#### 470 Methods

#### 471 Datasets

472 Based on the availability of the whole exome sequencing (WES) of germline gnomes, their paired tumor genomes, and paired RNA-seq data, 14 common cancer types were selected from TCGA (n=200 473 474 at least for each cancer type). To remove the effects of virus-infection for the NK cell study, we 475 removed the virus-infected tumors. Only 15% of the liver tumors (i.e., this number is too small to 476 conduct analysis) without virus infection, thus, we excluded this cancer type for further analysis. Thus, 477 13 common cancers used in this study were BLCA, BRCA, COAD, LGG, HNSC, KIRC, LUAD, 478 LUSC, PRAD, SKCM, STAD, THCA and UCEC. Because the primary melanoma samples were not 479 many, only metastatic SKCM samples were included for analysis. Distinct clinical subtypes have been 480 reported in breast cancer, thus we took only the ER+ breast tumors in this study, because the sample 481 numbers of HER2+ and triple negatives are small in TCGA. The WES files derived from buffy coats 482 (normal samples) of these cancer patients (n=5,883) were downloaded from TCGA, and the normalized 483 RNA-sequencing data with Root Mean Square Error (RMSE) across 13 types of cancers (n=5,373) 484 were downloaded from FireBrowse. The WES files of 4,500 non-cancer individuals (phs000473.v2.p2, 485 phs000806.v1.p1, phs001194.v2.p2) were downloaded from The database of Genotypes and 486 Phenotypes (dbGaP). RNA-sequencing data of 49 ICT-clinical trial melanoma sample and 47 ICT-487 clinical trial gastric samples were collected from GSE91061 and PRJEB25780, respectively, and were

- 488 processed based on the mRNA analysis pipeline in TCGA.
- 489

### 490 Variant calling and germline variant determination

491 For TCGA WES files, variant calling was performed using Varscan (version 2.3.9). The thresholds for 492 germline variant calls required variant allele fraction (VAF) between 45% and 55%, and >90%. 493 Functional variants were examined and annotated using the Combined Annotation Dependent 494 Depletion (CADD) using the default parameters. To keep the consistency with the TCGA pipeline for 495 processing WES data of the non-cancer individuals, BWA (version 0.7.15) was used to align with 496 default parameters, piping into Samtools (version 0.1.8) to sort. Additional adding read groups and 497 duplicate removal were processed with Picard-tools (version 2.6.0). The resulted BAM files were 498 processed with GATK (version 4.0.11.0) for realignment and base recalibration. Varscan (version 499 2.3.9) and CADD were used to call and annotate functional germline variants.

- 500
- 501
- 502

#### 503 Immune gene set and clustering analysis

504 Immune related genes (n=1,384) including MHC system-related genes [<sup>61</sup>], immunophenoscore-related 505 genes [<sup>14</sup>], ICT essential genes for immunotherapy [<sup>12</sup>] and cytotoxic T cell-resistant genes [<sup>62</sup>] were 506 collected and identified as critical immune-related genes (the gene pool *G*). RNA-sequencing data of 507 melanoma patients in TCGA were used to screen the key genes.

508

509 Step#1 Initialize the candidate set of key genes, that is,  $G_{candidate} = \phi$ .

510 Step#2 Randomly select 30% genes from G to form the gene set  $G_{random}$ .

511 Step#3 Replace the features of elements in the patient set P with  $G_{random}$  to form the sample set  $S_{random}$ .

512 Step#4 Group the samples in  $S_{random}$  by using the hierarchical clustering method. For each of the

- 513 clustering, clValid (<sup>63</sup>) was used to evaluate the clustering stability and the most stable clustering number
- 514 was recorded.
- 515 Step#5 Repeat Steps 2-4 100,000 times. Rank the most stable clustering numbers and select the most
  516 suitable clustering number 3.
- 517 Step#6 Extract the genes when clustering number is 3, and rank the genes. Select the most informative 518 genes and record them as the final set of key-gene candidates (1,294 genes).

519 We used the 1,294 genes to conduct unsupervised clustering analyses of the RNA-seq data for each 520 cancer type to define TIME subtypes.

521

# 522 TIL abundance calculation and pathway enrichment analysis

A deconvolution approach (<sup>14</sup>) was used to extract the abundance of each immune cell based on their gene markers from a tumor RNA-seq data. Pathway enrichment analysis was conducted using DAVID (https://david.ncifcrf.gov).

526

### 527 Assigning ICT trial samples into TIME subtypes

To assign an ICT-clinical trial sample into a TIME subtype, t-test statistics were first conducted in TIMErich vs TIME-intermediate and TIME-intermediate vs TIME-poor tumors' RNA-seq data for the genes derived from the NK cell-mediated cytotoxicity pathway and the Wnt signaling pathway. The significantly differential genes (p<0.05) were used for conduct K-nearest neighbors (KNN, k=5) to assign the sample to a TIME subtype. Spearman's rank correlation was conducted between the sample and the

533	samp	es in each TIME subtype based on the differential genes. TCGA-SKCM and TCGA-STAD samples
534	were	used for assigning the ICT-clinical trial samples of SKCM and STAD, respectively.
535		
536	Refer	rences
537 538 539	1.	Fallahpour S, Navaneelan T, De P, Borgo A. Breast cancer survival by molecular subtype: a population-based analysis of cancer registry data. <i>CMAJ open</i> 2017, <b>5</b> (3): E734-E739.
540 541 542	2.	Gao JJ, Swain SM. Luminal A Breast Cancer and Molecular Assays: A Review. <i>The oncologist</i> 2018, <b>23</b> (5): 556-565.
543 544 545 546	3.	Zaman N, Li L, Jaramillo ML, Sun Z, Tibiche C, Banville M, <i>et al.</i> Signaling network assessment of mutations and copy number variations predict breast cancer subtype-specific drug targets. <i>Cell reports</i> 2013, <b>5</b> (1): 216-223.
547 548 549 550 551	4.	Haque R, Ahmed SA, Inzhakova G, Shi J, Avila C, Polikoff J, <i>et al.</i> Impact of breast cancer subtypes and treatment on survival: an analysis spanning two decades. <i>Cancer epidemiology, biomarkers &amp; prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology</i> 2012, <b>21</b> (10): 1848-1855.
552 553 554	5.	Sharma P, Allison JP. The future of immune checkpoint therapy. <i>Science</i> 2015, <b>348</b> (6230): 56-61.
555 556 557	6.	Postow MA, Callahan MK, Wolchok JD. Immune Checkpoint Blockade in Cancer Therapy. <i>J Clin Oncol</i> 2015, <b>33</b> (17): 1974-U1161.
558 559 560 561	7.	Peng D, Kryczek I, Nagarsheth N, Zhao L, Wei S, Wang W, <i>et al.</i> Epigenetic silencing of TH1- type chemokines shapes tumour immunity and immunotherapy. <i>Nature</i> 2015, <b>527</b> (7577): 249- 253.
562 563 564 565	8.	Ribas A, Dummer R, Puzanov I, VanderWalde A, Andtbacka RHI, Michielin O, <i>et al.</i> Oncolytic Virotherapy Promotes Intratumoral T Cell Infiltration and Improves Anti-PD-1 Immunotherapy (vol 170, 1109.e1, 2017). <i>Cell</i> 2018, <b>174</b> (4): 1031-1032.
566 567 568	9.	Pahl J, Cerwenka A. Tricking the balance: NK cells in anti-cancer immunity. <i>Immunobiology</i> 2017, <b>222</b> (1): 11-20.
569 570 571 572	10.	Malmberg KJ, Carlsten M, Bjorklund A, Sohlberg E, Bryceson YT, Ljunggren HG. Natural killer cell-mediated immunosurveillance of human cancer. <i>Seminars in immunology</i> 2017, <b>31</b> : 20-29.
573 574 575	11.	Bryceson YT, Chiang SC, Darmanin S, Fauriat C, Schlums H, Theorell J, <i>et al.</i> Molecular mechanisms of natural killer cell activation. <i>Journal of innate immunity</i> 2011, <b>3</b> (3): 216-226.
576 577 578	12.	Patel SJ, Sanjana NE, Kishton RJ, Eidizadeh A, Vodnala SK, Cam M, <i>et al.</i> Identification of essential genes for cancer immunotherapy. <i>Nature</i> 2017, <b>548</b> (7669): 537-+.

- 13. Rock KL, Reits E, Neefjes J. Present Yourself! By MHC Class I and MHC Class II Molecules.
   *Trends Immunol* 2016, **37**(11): 724-737.
- 582 14. Charoentong P, Finotello F, Angelova M, Mayer C, Efremova M, Rieder D, *et al.* Pan-cancer
  583 Immunogenomic Analyses Reveal Genotype-Immunophenotype Relationships and Predictors
  584 of Response to Checkpoint Blockade. *Cell reports* 2017, 18(1): 248-262.
- Wang E, Zaman N, McGee S, Milanese JS, Masoudi-Nejad A, O'Connor-McCourt M.
  Predictive genomics: a cancer hallmark network framework for predicting tumor clinical
  phenotypes using genome sequencing data. *Seminars in cancer biology* 2015, **30:** 4-12.
- Jean-Sebastien Milanese CT, Naif Zaman, Jinfeng Zou, Pengyong Han, Zhi Gang Meng, Andre
   Nantel, Arnaud Droit, Edwin Wang. Germline genomic landscapes of breast cancer patients
   significantly predict clinical outcomes. *bioRxiv* 2018.
- Jean-Sebastien Milanese CT, Naif Zaman, Jinfeng Zou, Pengyong Han, Zhiganag Meng, Andre
  Nantel, Arnaud Droit, Edwin Wang. eTumorMetastasis, a network-based algorithm predicts
  clinical outcomes using whole-exome sequencing data of cancer patients. *bioRxiv*.
- 59818.Jinfeng Zou EW. eTumorRisk, an algorithm predicts cancer risk based on co-mutated gene599networks in an individual's germline genome. 2018.
- 601 19. Orange JS. Natural killer cell deficiency. *The Journal of allergy and clinical immunology* 2013, 132(3): 515-525.
- Mace EM, Orange JS. Genetic Causes of Human NK Cell Deficiency and Their Effect on NK
  Cell Subsets. *Frontiers in immunology* 2016, 7: 545.
- Mandal A, Viswanathan C. Natural killer cells: In health and disease. *Hematology/oncology and stem cell therapy* 2015, 8(2): 47-55.
- Long EO, Kim HS, Liu D, Peterson ME, Rajagopalan S. Controlling natural killer cell
  responses: integration of signals for activation and inhibition. *Annual review of immunology*2013, **31:** 227-258.
- Watzl C, Long EO. Signal transduction during activation and inhibition of natural killer cells.
   *Current protocols in immunology* 2010, Chapter 11: Unit 11 19B.
- 617 24. Moretta A, Bottino C, Vitale M, Pende D, Cantoni C, Mingari MC, *et al.* Activating receptors
  618 and coreceptors involved in human natural killer cell-mediated cytolysis. *Annual review of*619 *immunology* 2001, **19:** 197-223.
- Biassoni R. Human natural killer receptors, co-receptors, and their ligands. *Current protocols in immunology* 2009, Chapter 14: Unit 14 10.
- Abel AM, Yang C, Thakar MS, Malarkannan S. Natural Killer Cells: Development, Maturation,
  and Clinical Utilization. *Frontiers in immunology* 2018, **9:** 1869.

626

581

585

589

593

597

600

603

613

616

620

627 27. Neesse A, Bauer CA, Ohlund D, Lauth M, Buchholz M, Michl P, et al. Stromal biology and therapy in pancreatic cancer: ready for clinical translation? Gut 2018. 628 629 630 28. Bottcher JP, Bonavita E, Chakravarty P, Blees H, Cabeza-Cabrerizo M, Sammicheli S, et al. 631 NK Cells Stimulate Recruitment of cDC1 into the Tumor Microenvironment Promoting Cancer 632 Immune Control. Cell 2018, 172(5): 1022-1037 e1014. 633 634 29. Liang SZ, Xu KC, Niu LZ, Wang XH, Liang YQ, Zhang MJ, et al. Comparison of autogeneic 635 and allogeneic natural killer cells immunotherapy on the clinical outcome of recurrent breast 636 cancer. Oncotargets Ther 2017, 10: 4273-4281. 637 638 Mao Y, Qu O, Zhang Y, Liu J, Chen X, Shen K. The value of tumor infiltrating lymphocytes 30. 639 (TILs) for predicting response to neoadjuvant chemotherapy in breast cancer: a systematic 640 review and meta-analysis. PloS one 2014, 9(12): e115103. 641 642 31. Denkert C. Loibl S. Noske A. Roller M. Muller BM. Komor M. et al. Tumor-associated 643 lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast 644 cancer. J Clin Oncol 2010, 28(1): 105-113. 645 Oda N. Shimazu K. Naoi Y. Morimoto K. Shimomura A. Shimoda M. et al. Intratumoral 646 32. 647 regulatory T cells as an independent predictive factor for pathological complete response to 648 neoadjuvant paclitaxel followed by 5-FU/epirubicin/cvclophosphamide in breast cancer 649 patients. Breast cancer research and treatment 2012, 136(1): 107-116. 650 651 33. Miyashita M, Sasano H, Tamaki K, Chan M, Hirakawa H, Suzuki A, et al. Tumor-infiltrating 652 CD8+ and FOXP3+ lymphocytes in triple-negative breast cancer: its correlation with 653 pathological complete response to neoadjuvant chemotherapy. Breast cancer research and 654 treatment 2014, 148(3): 525-534. 655 Azimi F, Scolyer RA, Rumcheva P, Moncrieff M, Murali R, McCarthy SW, et al. Tumor-656 34. infiltrating lymphocyte grade is an independent predictor of sentinel lymph node status and 657 658 survival in patients with cutaneous melanoma. J Clin Oncol 2012, 30(21): 2678-2683. 659 660 35. Li LY, Cui JW, Wang C, Wang YZ, Niu C, Yao C, et al. Adoptive transfer of NK cells in 661 combination with chemotherapy to improve outcomes of patients with locally advanced colon 662 carcinoma. J Clin Oncol 2017, 35. 663 Multhoff MSEPBNLYYMIGBMG. P04.02 Adoptive transfer of lymphokine activated NK cells 664 36. 665 in combination with anti-PD-1 immune checkpoint inhibitor in therapy of glioblastoma. Neuro-666 *Oncology*, **20**(suppl 3): iii278. 667 668 37. Spranger S, Bao R, Gajewski TF. Melanoma-intrinsic beta-catenin signalling prevents anti-669 tumour immunity. Nature 2015, 523(7559): 231-235. 670 671 38. Grasso CS, Giannakis M, Wells DK, Hamada T, Mu XJ, Quist M, et al. Genetic Mechanisms of 672 Immune Evasion in Colorectal Cancer. *Cancer discovery* 2018, **8**(6): 730-749. 673 20

- Imai K, Matsuyama S, Miyake S, Suga K, Nakachi K. Natural cytotoxic activity of peripheralblood lymphocytes and cancer incidence: an 11-year follow-up study of a general population. *Lancet* 2000, **356**(9244): 1795-1799.
- Montelli TC, Peracoli MT, Gabarra RC, Soares AM, Kurokawa CS. Familial cancer: depressed
  NK-cell cytotoxicity in healthy and cancer affected members. *Arquivos de neuro-psiquiatria*2001, **59**(1): 6-10.
- 41. Strayer DR, Carter WA, Brodsky I. Familial occurrence of breast cancer is associated with
  reduced natural killer cytotoxicity. *Breast cancer research and treatment* 1986, 7(3): 187-192.
- Bovbjerg DH, Valdimarsdottir H. Familial cancer, emotional distress, and low natural cytotoxic
  activity in healthy women. *Annals of oncology : official journal of the European Society for Medical Oncology* 1993, 4(9): 745-752.
- Ballas ZK, Buchta CM, Rosean TR, Heusel JW, Shey MR. Role of NK cell subsets in organspecific murine melanoma metastasis. *PloS one* 2013, 8(6): e65599.
- 692 44. Ohkuma T, Peters SAE, Woodward M. Sex differences in the association between diabetes and
  693 cancer: a systematic review and meta-analysis of 121 cohorts including 20 million individuals
  694 and one million events. *Diabetologia* 2018, **61**(10): 2140-2154.
- 45. Steele CB, Thomas CC, Henley SJ, Massetti GM, Galuska DA, Agurs-Collins T, *et al.* Vital
  Signs: Trends in Incidence of Cancers Associated with Overweight and Obesity United States,
  2005-2014. *MMWR Morbidity and mortality weekly report* 2017, **66**(39): 1052-1058.
- Gross AL, Gallo JJ, Eaton WW. Depression and cancer risk: 24 years of follow-up of the
  Baltimore Epidemiologic Catchment Area sample. *Cancer causes & control : CCC* 2010,
  21(2): 191-199.
- 47. Batty GD, Russ TC, Stamatakis E, Kivimaki M. Psychological distress in relation to site
  specific cancer mortality: pooling of unpublished data from 16 prospective cohort studies. *Bmj*2017, **356:** j108.
- 48. Bahr I, Jahn J, Zipprich A, Pahlow I, Spielmann J, Kielstein H. Impaired natural killer cell subset phenotypes in human obesity. *Immunologic research* 2018, 66(2): 234-244.
  710
- 49. O'Shea D, Cawood TJ, O'Farrelly C, Lynch L. Natural killer cells in obesity: impaired function
  and increased susceptibility to the effects of cigarette smoke. *PloS one* 2010, **5**(1): e8660.
- 50. Wyman PA, Moynihan J, Eberly S, Cox C, Cross W, Jin X, *et al.* Association of family stress
  with natural killer cell activity and the frequency of illnesses in children. *Archives of pediatrics & adolescent medicine* 2007, **161**(3): 228-234.
- 718 51. Riaz N, Havel JJ, Makarov V, Desrichard A, Urba WJ, Sims JS, *et al.* Tumor and
  719 Microenvironment Evolution during Immunotherapy with Nivolumab. *Cell* 2017, **171**(4): 934720 949 e916.
- 721

677

681

684

688

695

699

703

707

713

- 52. Kim ST, Cristescu R, Bass AJ, Kim KM, Odegaard JI, Kim K, *et al.* Comprehensive molecular
  characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer. *Nat Med*2018, 24(9): 1449-+.
- 72653.Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. *Nature*7272017, **541**(7637): 321-330.
- 54. Wargo JA, Reddy SM, Reuben A, Sharma P. Monitoring immune responses in the tumor
  microenvironment. *Current opinion in immunology* 2016, 41: 23-31.
- 55. Dunn GP, Dunn IF, Curry WT. Focus on TILs: Prognostic significance of tumor infiltrating
  lymphocytes in human glioma. *Cancer immunity* 2007, 7: 12.
- 56. Eerola AK, Soini Y, Paakko P. A high number of tumor-infiltrating lymphocytes are associated
  with a small tumor size, low tumor stage, and a favorable prognosis in operated small cell lung
  carcinoma. *Clin Cancer Res* 2000, 6(5): 1875-1881.
- 57. Vesely MD, Kershaw MH, Schreiber RD, Smyth MJ. Natural innate and adaptive immunity to cancer. *Annual review of immunology* 2011, 29: 235-271.
- 58. Crispo A, Brennan P, Jockel KH, Schaffrath-Rosario A, Wichmann HE, Nyberg F, *et al.* The cumulative risk of lung cancer among current, ex- and never-smokers in European men. *British journal of cancer* 2004, **91**(7): 1280-1286.
- 59. Brennan P, Crispo A, Zaridze D, Szeszenia-Dabrowska N, Rudnai P, Lissowska J, *et al.* High
  cumulative risk of lung cancer death among smokers and nonsmokers in Central and Eastern
  Europe. *American journal of epidemiology* 2006, **164**(12): 1233-1241.
- Bjorkstrom NK, Ljunggren HG, Michaelsson J. Emerging insights into natural killer cells in human peripheral tissues. *Nature reviews Immunology* 2016, 16(5): 310-320.
- Rock KL, Reits E, Neefjes J. Present Yourself! By MHC Class I and MHC Class II Molecules.
   *Trends in immunology* 2016, **37**(11): 724-737.
- Pan D, Kobayashi A, Jiang P, de Andrade LF, Tay RE, Luoma AM, *et al.* A major chromatin regulator determines resistance of tumor cells to T cell-mediated killing. *Science* 2018, 359(6377): 770-+.
- Brock G, Datta S, Pihur V, Datta S. clValid: An R package for cluster validation. *J Stat Softw*2008, 25(4): 1-22.
- 762 763

759

725

728

731

734

738

741

745

749

- 761
- 764
- 765
- 766
- ----
- 767

# 768769 Figure Legends

770

771 Figure 1. Clinical and cellular characteristics of the TIME subtypes. (a) Representative heatmaps 772 derived from the gene expression of the immune-checkpoint therapy (ICT) essential genes, showing the 773 universal TIME subtypes in breast invasive carcinoma (BRCA), lung adenocarcinoma (LUAD) and 774 skin cutaneous Melanoma (SKCM). The heatmaps for other cancer types are shown in Supplementary 775 Figure 1; (b) Abundance of infiltrated immune cells in TIME subtypes across 12 types of cancers; (c) 776 Kaplan–Meier curves of the patient groups between the TIME-rich subtype and the combined TIME-777 intermediate and -poor subtypes, revealing that the survival time for the patients in the TIME-rich 778 subtype is significantly longer than those in the TIME-intermediate and -poor subtypes; and (d) 779 Pathway enriched analysis derived from the significantly differential genes of RNA-seq data between 780 the TIME-rich subtype and the TIME-intermediate and -poor subtypes. The digital numbers represent 781 FDR-corrected p values. 782 783 Figure 2. Heatmaps representing the enrichment pathways derived from functional germline 784 genomic variants. (a) A heatmap shows the significantly enriched pathways derived from the 785 significantly differential germline variants between TIME-rich and TIME-intermediate-poor subtypes 786 in 13 cancer types. (b) A heatmap shows the significantly enriched pathways derived from the 787 significantly differential germline variants between non-cancer individuals and TIME-intermediate-

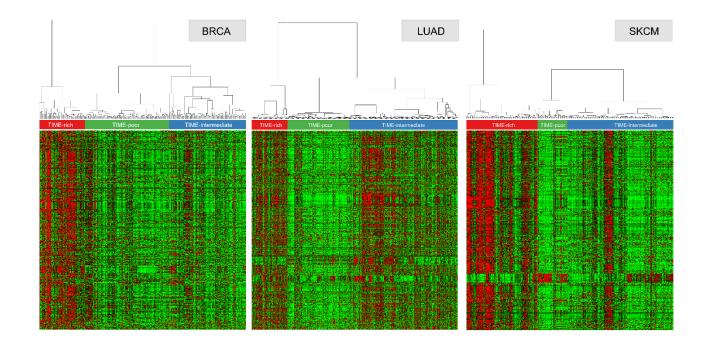
poor patients in 13 cancer types. The digital numbers represent FDR-corrected p values.

789

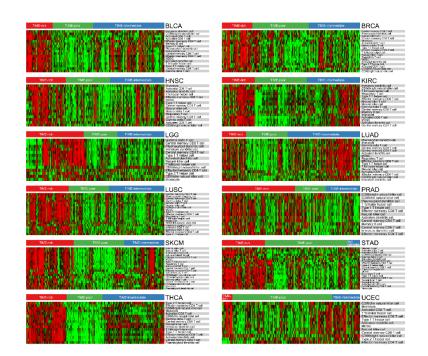
790 Figure 3. The associations between the inherited detected NK cells and clinical outcomes, and the 791 abundance of infiltrated immune cells in TIMEs. (a) Kaplan–Meier curves of the patient groups of 792 the high- and low-number of functionally inherited variants in the NK cells for disease-free survival. 793 Patients were top-to-bottom ranked based on the number of functionally inherited variants in NK cells. 794 Top 40% and bottom 40% of the ranked patients were defined as high- and low-number of the NK cell 795 defected patient groups, respectively. (b) Negative correlations between the number of the NK cell 796 inheritable defected and the abundance of the infiltrated immune cells in TIMEs. Breast invasive 797 carcinoma (BRCA), lung adenocarcinoma (LUAD) and skin cutaneous Melanoma (SKCM). The 798 survival differences for other types of cancer are shown in Supplementary Figure 6. \*p-value >0.05; 799 \*\*0.05>p-value >0.001; and \*\*\*p-value<0.001. The NK-specific-genes included NKD genes and NK

- 800 receptors/ligands of the 103 defected NK cell genes, while the NK-immune-universal-genes included
- the global immune cell genes and the universal genes of the 103 defected NK cell genes.

- 810 Fig 1a



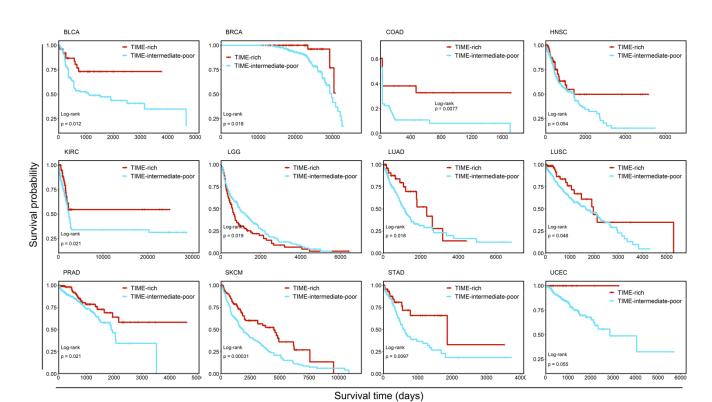
- 815 Fig 1b





- \_ . \_

820 Fig 1c





- -

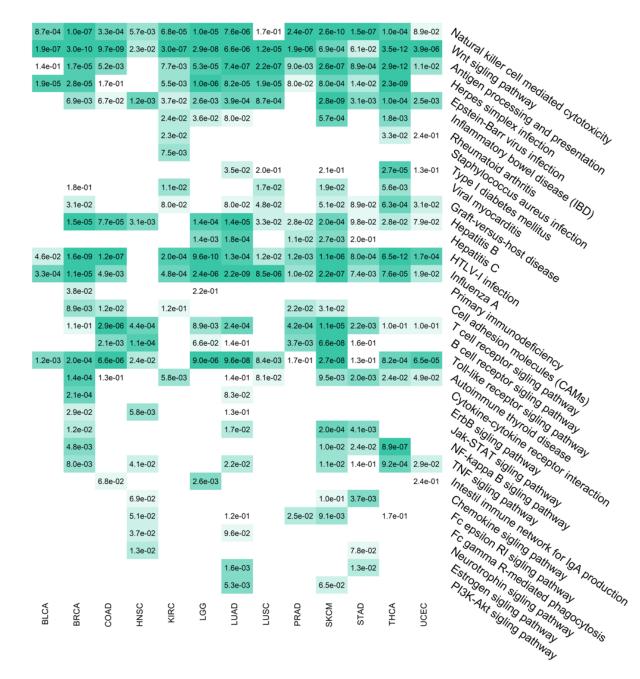
# 

# 829 Fig 1d

12e-174.5e-201.2e-011.4e-173.3e-173.3e-171.5e-111.1e-172.4e-011.4e-174.5e-163.5e-171.4e-085.4e-196.0e-222.0e-232.0e-122.0e-122.0e-127.7e-202.8e-232.8e-253.0e-237.8e-227.8e-123.0e-173.0e-172.8e-232.8e-253.0e-238.7e-237.8e-123.0e-174.8e-121.2e-114.7e-123.0e-172.8e-232.8e-253.0e-122.8e-122.8e-123.6e-122.8e-123.0e-172.8e-123.6e-122.8e-123.0e-173.0e-173.0e-173.0e-173.0e-172.8e-123.6e-172.8e-123.6e-171.2e-053.6e-173.6e-1													
12e-174.5e-201.2e-011.4e-173.3e-173.3e-171.5e-111.1e-172.4e-011.4e-174.5e-163.5e-171.4e-085.4e-196.0e-222.0e-232.0e-122.0e-122.0e-127.7e-222.8e-232.8e-332.8e-232.8e-332.8e-232.8e-332.8e-332.8e-332.8e-332.8e-3													6.4e-32
3.5e-18         8.6e-17         3.0e-14         4.4e-26         1.2e-10         8.2e-20         6.2e-20         7.2e-10         2.4e-01         2.4e-01         2.4e-01         8.2e-20         7.2e-10         2.4e-01         2.4e-01         8.2e-20         7.2e-10         2.4e-01         3.2e-10         2.4e-13         3.0e-15         3.0e-15         3.0e-15         3.2e-10         1.2e-10         3.2e-10         1.2e-10         3.2e-10         1.2e-10         3.2e-10         3.2e-10         1.2e-10         3.2e-10         3.2e-10         3.2e-10         3.2e-10         3.2e-10         3.2e-10         3.2e-17         7.1e-05         3.2e-10         3.2e-17         7.2e-11         3.2e-10         3.2e-17         7.2e-11         3.2e-10         3.2e-17         7.2e-11         3.2e-10         3.2e-17         3.2e-17 <t< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>1.0e-38</td></t<>													1.0e-38
12e-174.5e-201.2e-011.2e-133.0e-173.0e-173.0e-171.1e-172.4e-011.4e-174.5e-163.5e-171.4e-085.4e-196.0e-222.0e-022.0e-122.0e-122.0e-127.7e-202.8e-232.8e-232.8e-232.8e-227.8e-127.8e-323.0e-177.4e-222.8e-173.0e-144.4e-261.2e-193.7e-223.8e-184.1e-152.8e-206.8e-227.8e-133.0e-173.0e-174.5e-118.7e-133.3e-141.3e-226.7e-117.2e-131.0e-072.8e-025.8e-122.8e-021.2e-052.8e-022.8e-032.8e-032.6e-072.8e-032.6e-071.2e-053.6e-171.2e-053.5e-171.2e-051.2e-051.2e-051.2e-053.6e-171.2e-053.8e-181.2e-041.2e-051.2e-051.2e-051.2e-051.2e-053.8e-171.2e-053.8e-171.2e-053.8e-171.2e-051.2e-051.2e-051.2e-051.2e-051.2e-051.2e-051.2e-051.2e-051.2e-051.2e-051.2e-051.2e-053.8e-171.2e-051.2e-051.2e-053.8e-072.9e-071.2e-051.2e-053.2e-073.8e-052.9e-071.2e-051.2e-053.8e-072.9e-071.2e-051.2e-053.2e-073.8e-052.9e-071.2e-051.2e-053.8e-051.2e-051.2e-053.2e-073.2e-052.2e-073.8e-052.9e-071.2e-053.2e-073.2e-073.2e	2.00 00	0.10 12	0.10 12		0.00.00						3.6e-32	1.10 10	4.9e-19
12e-174.5e-201.2e-011.2e-101.2e-171.2e-171.2e-171.2e-171.4e-174.5e-163.5e-171.4e-185.4e-196.0e-222.0e-032.0e-132.0e-133.0e-173.7e-203.8e-232.8e-233.8e-232.8e-233.8e-232.8e-233.8e-133.7e-233.2e-123.2e-123.2e-123.2e-123.2e-133.2e-1							3.3e-12	1.9e-12	8.2e-22	5.3e-18			6.2e-17
12e-174.5e-201.2e-011.2e-17 <th< td=""><td>3.6e-20</td><td>9.4e-23</td><td>1.3e-14</td><td>9.0e-23</td><td>7.1e-20</td><td>8.1e-22</td><td>1.3e-20</td><td>1.2e-17</td><td>1.0e-16</td><td>2.5e-26</td><td></td><td>6.7e-25</td><td>9.0e-22</td></th<>	3.6e-20	9.4e-23	1.3e-14	9.0e-23	7.1e-20	8.1e-22	1.3e-20	1.2e-17	1.0e-16	2.5e-26		6.7e-25	9.0e-22
12e-174.5e-201.2e-011.2e-071.2e-071.2e-071.2e-171.2e-172.4e-011.4e-174.5e-163.5e-171.4e-085.4e-196.0e-222.0e-032.0e-132.0e-133.0e-173.7e-223.8e-232.8e-233.8e-232.8e-233.8e-133.7e-223.8e-133.7e-223.8e-133.7e-223.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-133.8e-133.8e-133.7e-133.8e-133.8e-133.7e-133.8e-143.8e-143.8e-143.8e-143.8e-143.8e-143.8e-143.8e-143.8e-143.8e-143.8e-143.8e-143.8e-143.8e-143.8e-153.8e-153.8e-153.8e-153.8e-153.8e-153.8e-153.8e-153.8e-1	6.4e-06	9.0e-03	2.4e-05	9.5e-05	1.5e-04	3.1e-03	3.6e-04	9.0e-03	2.0e-07	5.9e-04		1.9e-04	1.3e-07
12e-174.5e-201.2e-001.4e-133.0e-173.3e-181.5e-111.1e-172.4e-011.4e-174.5e-163.5e-171.4e-085.4e-196.0e-222.0e-032.0e-132.0e-133.0e-173.7e-223.8e-233.8e-233.8e-233.8e-233.8e-233.8e-233.8e-233.8e-233.8e-233.8e-133.7e-223.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.7e-143.7e-133.7e-1	6.5e-20	2.8e-18	7.9e-05	1.2e-18	1.8e-14	3.4e-20	2.8e-14	2.4e-18	7.1e-06	6.6e-16	2.4e-10	1.4e-18	2.9e-13
1.2e-174.5e-201.2e-011.4e-172.4e-011.4e-172.4e-174.5e-163.5e-171.4e-085.4e-196.0e-228.0e-032.6e-186.3e-197.7e-201.5e-192.5e-199.7e-027.3e-217.4e-222.3e-133.3e-183.3e-183.3e-183.3e-183.2e-121.7e-343.7e-223.8e-233.8e-233.8e-233.8e-233.8e-233.8e-133.7e-233.2e-121.2e-014.8e-021.2e-021.2e-014.5e-118.7e-133.3e-181.3e-226.7e-117.2e-131.0e-172.1e-092.8e-232.6e-32.6e-071.2e-021.2e-013.9e-171.6e-073.8e-031.4e-131.3e-021.6e-041.2e-055.8e-112.8e-005.6e-132.6e-071.2e-053.5e-171.6e-071.6e-031.2e-041.2e-051.2e-051.2e-053.3e-162.8e-073.3e-161.2e-051.3e-072.6e-072.6e-072.6e-072.6e-072.6e-072.6e-073.3e-062.9e-072.1e-031.2e-161.0e-071.2e-051.2e-051.2e-051.2e-053.6e-177.6e-153.2e-173.6e-072.6e-073.	1.4e-13	3.7e-15	2.1e-01	2.9e-13	1.3e-12	1.4e-13	1.4e-11	3.2e-16	3.8e-04	3.4e-17		2.3e-17	2.8e-06
12e-174.5e-201.2e-011.4e-133.0e-173.3e-181.5e-111.1e-172.4e-011.4e-174.5e-163.5e-171.4e-085.4e-196.0e-222.0e-032.0e-132.0e-133.0e-173.7e-223.6e-233.6e-132.6e-031.2e-021.2e-033.0e-154.5e-118.6e-133.3e-143.6e-051.6e-051.6e-012.6e-032.6e-032.6e-032.6e-031.2e-053.6e-17<			1.0e-03		5.5e-04								4.2e-03
12e-174.5e-201.2e-011.2e-071.2e-071.2e-071.2e-171.2e-172.4e-011.4e-174.5e-163.5e-171.4e-085.4e-196.0e-222.0e-032.0e-132.0e-133.0e-173.7e-223.8e-232.8e-233.8e-232.8e-233.8e-133.7e-223.8e-133.7e-223.8e-133.7e-223.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-233.8e-133.7e-133.8e-133.8e-133.7e-133.8e-133.8e-133.7e-133.8e-143.8e-143.8e-143.8e-143.8e-143.8e-143.8e-143.8e-143.8e-143.8e-143.8e-143.8e-143.8e-143.8e-143.8e-153.8e-153.8e-153.8e-153.8e-153.8e-153.8e-153.8e-153.8e-1	6.3e-10	2.1e-10		7.2e-07		3.8e-09		5.9e-02		4.0e-10		5.7e-10	2.3e-02
1.2e-174.5e-201.2e-011.4e-172.4e-011.4e-172.4e-174.5e-163.5e-171.4e-085.4e-196.0e-228.0e-032.6e-186.3e-197.7e-201.5e-192.5e-199.7e-027.3e-217.4e-222.3e-133.3e-183.3e-183.3e-183.3e-183.2e-121.7e-343.7e-223.8e-233.8e-233.8e-233.8e-233.8e-233.8e-133.7e-233.2e-121.2e-014.8e-021.2e-021.2e-014.5e-118.7e-133.3e-181.3e-226.7e-117.2e-131.0e-172.1e-092.8e-232.6e-32.6e-071.2e-021.2e-013.9e-171.6e-073.8e-031.4e-131.3e-021.6e-041.2e-055.8e-112.8e-005.6e-132.6e-071.2e-053.5e-171.6e-071.6e-031.2e-041.2e-051.2e-051.2e-053.3e-162.8e-073.3e-161.2e-051.3e-072.6e-072.6e-072.6e-072.6e-072.6e-072.6e-073.3e-062.9e-072.1e-031.2e-161.0e-071.2e-051.2e-051.2e-051.2e-053.6e-177.6e-153.2e-173.6e-072.6e-073.	4.8e-05	7.6e-05		1.7e-03	4.7e-04	1.4e-04	3.5e-05	4.6e-05		5.3e-05		2.6e-03	
3be-16         8.7e-17         30e-14         4.3e-26         1.2e-19         4.3e-19         8.6e-18         4.1e-15         2.8e-20         6.8e-27         7.8e-27         4.8e-27         7.8e-27         3.8e-27         3.8e-27         3.0e-15	1.2e-17	4.5e-20	1.2e-01	1.4e-13	3.0e-17	3.3e-18	1.5e-11	1.1e-17	2.4e-01	1.4e-17	4.5e-16	3.5e-17	1.4e-08
3be-16         8.7e-17         30e-14         4.3e-26         1.2e-19         4.3e-19         8.6e-18         4.1e-15         2.8e-20         6.8e-27         7.8e-27         4.8e-27         7.8e-27         3.8e-27         3.8e-27         3.0e-15	5.4e-19	6.0e-22	8.0e-03	2.6e-18	6.3e-19	7.7e-20	1.0e-14	2.5e-19	9.7e-02	7.3e-21		3.3e-19	5.2e-10
3be-16         8.8e-17         30e-14         4.3e-26         1.2e-19         4.3e-19         8.6e-17         4.1e-15         2.8e-20         6.8e-20         6.8e-30         1.2e-01         1.2e-01 <th1.2e-01< th=""> <th1.2e-01< th=""> <th1.2< td=""><td>7.4e-22</td><td>2.2e-30</td><td>2.3e-12</td><td>1.7e-34</td><td>3.3e-31</td><td>3.7e-22</td><td>3.8e-23</td><td>2.8e-25</td><td>3.0e-23</td><td>8.7e-23</td><td></td><td>7.8e-32</td><td>3.1e-28</td></th1.2<></th1.2e-01<></th1.2e-01<>	7.4e-22	2.2e-30	2.3e-12	1.7e-34	3.3e-31	3.7e-22	3.8e-23	2.8e-25	3.0e-23	8.7e-23		7.8e-32	3.1e-28
1.0-18         1.0-18         6.1e-17         7.6-17         8.2e-10         3.2e-12         3.6-02         9.2e-19         6.8e-11         7.3e-17         2.6e-79           1.2e-08         4.2e-10         2.7e-14         8.2e-17         1.8e-15         1.3e-10         1.0e-16         3.1e-09         1.7e-17         3.9e-09         1.3e-09         4.6e-11         1.5e-16           1.5e-16         1.9e-10         7.2e-11         1.4e-10         4.2e-11         1.7e-03         2.2e-07         1.9e-08         3.5e-06         8.1e-07         2.6e-07         1.5e-16         8.2e-07         3.5e-06         8.1e-07         2.6e-07         1.5e-17         8.3e-07         2.5e-06         8.2e-07         3.5e-06         8.1e-07         2.5e-07         8.2e-07         3.5e-07         8.2e-07         3.5e-07         8.2e-07         3.6e-07         1.6e-07         1.6e-07         1.6e-07         1.6e-07         1.6e-07         3.6e-07         1.6e-07         1.6e-07         3.6e-07         3.6e-07         2.6e-07         3.6e-07         3.6e-07         3.6e-07         3.6e-07	3.5e-18	8.8e-17	3.0e-14	4.4e-26	1.2e-19	4.3e-19	8.6e-18	4.1e-15	2.8e-20	6.8e-22			1.2e-01
1.2.161.0.185.1.177.6.178.2.171.2.102.0.103.5.029.2.106.8.117.3.0.72.6.071.2.2.044.2.102.2.111.2.111.2.111.0.111.0.103.1.001.7.173.0.001.3.0.04.0.101.5.111.2.2.101.2.111.4.104.2.111.7.002.2.001.2.0.02.2.013.3.004.0.105.7.001.3.004.0.007.0.007.0.007.9.002.2.007.1.002.2.001.0.008													3.0e-15
1.2.161.0.185.1.177.6.178.2.173.2.172.0.163.5.2.09.2.196.8.117.3.172.6.101.2.2.044.2.2.171.8.2.171.8.2.171.8.2.171.8.2.171.0.2.13.1.2.013.1.2.013.2.2													3.5e-12
10-18         10-18         6 16-17         7.6-18         8.2-6         3.2-12         3.6-02         9.2-19         6.8-11         7.3-7         2.6-09           1.2-08         4.2-10         2.7-14         8.2-17         1.8-15         1.3-10         1.0-16         3.1-09         1.7-17         3.9-09         1.3-09         4.6-11         1.5-16           1.6-14         1.9-12         2.1-00         7.2-11         1.4-10         4.2-11         1.7-03         2.0-10         8.2-03         2.2-12         3.3-09         4.0-10         5.7-06           1.9-04         4.0-00         7.2-11         1.4-00         2.2-07         1.9-08         3.6-06         8.1-07         2.0-01         8.2-03         3.2-07         3.2-08         8.2-07         3.2-09         2.2-12         3.3-09         4.2-10         3.2-09           2.3-04         4.0-01         5.0-12         5.0-12         2.1-00         7.2-03         1.2-07         3.2-03         3.2-09         2.2-01         3.2-03         3.2-01         1.2-01         3.2-01         1.2-01         3.2-01         1.2-01         3.2-01         1.2-01         3.2-01         1.2-01         3.2-01         3.2-01         1.2-01         3.2-01         3.2-01         1.2-0													0.00 12
10-16         10-17         61-17         7 ien 3         8 i					0.00-00	2.00-03	2.00-01		2.00-00	0.06-03		1.00-01	
12e-16         10e-18         16e-17         7.6e-76         8.2e-76         3.2e-12         2.6e-76         3.6e-70         9.2e-76         6.8e-17         7.8e-76         1.8e-75         1.8e-75         1.8e-76         1.8e-76         1.8e-76         1.8e-76         1.8e-76         1.8e-76         1.7e-77         3.9e-70         1.3e-70         4.8e-77         4.8e-77         1.8e-75         1.8e-77         1.7e-73         2.9e-70         3.9e-70         1.3e-70         4.9e-70         2.2e-70         3.9e-70         1.3e-70         4.9e-70         2.2e-70         3.9e-70         3.3e-70         4.9e-70         4.9e-70         2.2e-70         3.9e-70         3.3e-70         4.9e-70         4.9e-70         2.7e-70         3.9e-70	3.60.07	4.06.02			0.80.04	1.40.02	3.00.04	5.60.04	3.00.10	1.20.04	1.10.02	5 30 00	9.90.00
10-18         10-18         6         10-17         6         10-18         10-18         6         10-17         10-18         10-18         10-16         10-16         10-16         10-16         10-16         10-17         10-17         10-18         10-18         10-17         10-17         10-18         10-18         10-16         10-16         10-16         10-17         10-18         10-18         10-16			1.86-06						3.9e-10				0.00-00
No.cold         No.cold <t< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>2 5 . 00</td><td></td><td></td><td></td><td>2.1e-03</td></t<>									2 5 . 00				2.1e-03
No.col         No.col<			07.41						_				2.66-09
No.col         No.col<													1.5e-16
No.col         No.col<										_			6.7e-06
No.col         No.col<			1.1e-06				2.4e-03		1.9e-08				2.0e-10
No.cold         No.cold <t< td=""><td>2.3e-06</td><td>4.0e-09</td><td></td><td>6.0e-04</td><td>1.6e-03</td><td>2.1e-06</td><td></td><td>3.1e-07</td><td></td><td>8.9e-10</td><td>2.5e-05</td><td>8.3e-08</td><td></td></t<>	2.3e-06	4.0e-09		6.0e-04	1.6e-03	2.1e-06		3.1e-07		8.9e-10	2.5e-05	8.3e-08	
1.6.05         5.6.04         2.10e0         1.0.02         2.6.06         2.6.06         2.6.02 <th2.6.02< th=""> <th2.6.02< th="">         2.6.02<!--</td--><td>3.5e-06</td><td>1.1e-02</td><td>1.3e-11</td><td>5.0e-15</td><td>5.8e-10</td><td>2.9e-06</td><td>7.4e-08</td><td>7.6e-06</td><td>1.5e-11</td><td>1.9e-04</td><td>4.1e-03</td><td>4.0e-05</td><td>2.8e-09</td></th2.6.02<></th2.6.02<>	3.5e-06	1.1e-02	1.3e-11	5.0e-15	5.8e-10	2.9e-06	7.4e-08	7.6e-06	1.5e-11	1.9e-04	4.1e-03	4.0e-05	2.8e-09
1         1         2         5         6         6         6         6         6         6         6         6         6         7 <th7< th="">         7         7         7</th7<>	1.5e-02		4.0e-06	4.8e-08	7.2e-05	3.6e-03	4.3e-05	7.7e-03	1.3e-09			2.0e-04	1.2e-07
1.6.05         5.6.04         2.1.05         1.0.05         2.6.06         2.6.06         2.6.07	1.1e-09	1.7e-08	1.5e-11	3.8e-12	1.0e-14	3.8e-08	4.1e-08	1.0e-07	1.1e-16	1.8e-08	9.1e-07	3.7e-14	1.0e-11
1.6.05         5.6-04         2.10-05         1.0-02         2.0-06         2.0-07         2.10-05         2.	1.5e-02	8.2e-02	3.6e-03	1.8e-07	1.5e-04	3.2e-05	2.8e-03	7.3e-02	8.0e-06	2.4e-02		4.9e-03	1.1e-02
1.6.05         5.6-04         2.10-05         1.0-02         2.0-06         2.0-07         2.10-05         2.	2.1e-04	4.0e-04	1.1e-07	3.4e-05	3.7e-08	7.3e-05	1.8e-02	6.0e-02	7.9e-07	2.7e-03		5.5e-03	5.3e-06
3.2.2.12         1.0.2.10         2.2.2.00         2.1.2.10         3.2.2.00			1.2e-05	5.5e-04	2.1e-06		1.0e-02		2.4e-06			2.1e-02	8.7e-06
2.50-08         1.10-09         6.16-05         5.30-08         6.30-00         1.80-07         2.50-07         2.20-07         1.20-07         2.20-07         1.20-07         2.20-07         1.40-07         2.20-07         1.40-07         2.20-07         1.40-07         2.20-07         1.40-07         2.20-07         1.40-07         2.20-07         1.40-07         2.20-07         1.40-07         2.20-07         1.40-07         2.20-07         1.40-07         2.20-07         1.40-07         2.20-07         1.40-07         2.20-07         1.40-07         2.20-07         1.40-07         2.20-07         1.40-07         2.20-07         1.40-07         2.20-17         1.40-07         2.20-17         2.20-17         1.60-07         2.20-18         2.20-17 <t< td=""><td>3.2e-12</td><td>1.0e-16</td><td>2.2e-02</td><td>2.1e-15</td><td>3.9e-14</td><td>1.4e-13</td><td>3.4e-09</td><td>3.0e-18</td><td></td><td>8.4e-21</td><td>3.4e-17</td><td>7.1e-25</td><td>4.7e-19</td></t<>	3.2e-12	1.0e-16	2.2e-02	2.1e-15	3.9e-14	1.4e-13	3.4e-09	3.0e-18		8.4e-21	3.4e-17	7.1e-25	4.7e-19
1.0001         8.9002         5.9007         3.9007         2.9007         9.2007	2.5e-08	1.1e-06	6.1e-05	5.3e-08	8.6e-05	1.8e-07	2.5e-02	1.7e-07	2.2e-06	1.2e-08	9.7e-03	4.0e-09	1.5e-02
2.5e-01       3.2e-01       3.2e-01       3.2e-01       3.2e-01       5.0e-00       5.0e-07       7.6e-03       6.6e-12       2.3e-04       9.0e-06       6.9e-11         6.4e-11       4.2e-15       9.3e-05       2.5e-06       1.6e-05       9.8e-06       1.2e-03       4.3e-12       2.5e-08       1.2e-15       2.0e-14       1.7e-08         2.2e-01       1.6e-05       4.3e-02       2.6e-02       8.9e-03       4.4e-02       7.0e-04       4.3e-02       2.4e-03       4.9e-03       4.9e-03       5.9e-03       1.9e-05       3.3e-01       4.9e-04       4.9e-02       4.9e-03       5.9e-03       4.9e-03       5.9e-03       1.9e-05       4.3e-04       4.9e-02       4.9e-03       5.9e-03       4.9e-04       4.9e-03       5.9e-03       4.9e-03       5.9e-03       1.9e-05       4.9e-03       5.9e-03       1.9e-04       4.9e-04       1.9e-04       4.9e-03       1.9e-03       1.9e-04       4.9e-03       1.9e-05       1.9e-05 <t< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>2.6e-04</td><td>9.8e-08</td></t<>												2.6e-04	9.8e-08
6.2e-05       5.5e-03       5.9e-10       3.5e-09       2.1e-05       6.0e-07       7.6e-03       6.6e-12       2.3e-04       9.0e-06       6.9e-11         6.4e-11       4.2e-15       9.3e-05       2.5e-06       1.6e-05       9.8e-08       1.2e-03       4.3e-12       2.5e-08       1.2e-15       2.0e-14       1.7e-08         2.2e-01       1.6e-02       1.4e-05       3.3e-02       2.6e-02       8.6e-02       7.6e-04       4.3e-04       6.9e-02       2.4e-05       4.9e-06       5.9e-02       3.4e-02       7.0e-04       4.3e-04       6.9e-02       2.4e-05       4.9e-06       5.9e-02       3.4e-02       7.0e-04       4.3e-04       4.9e-06       3.4e-02       4.9e-06       3.4e-02       4.9e-06       3.4e-02       4.9e-06       3.4e-02       4.9e-06       4.9e-06       3.4e-02       4.9e-06       3.4e-02       4.9e-06       3.8e-06       3.8e-06       3.2e-07       3.6e-07       1.0e-07       2.8e-09       3.5e-08       1.8e-04       3.2e-07       3.6e-07       1.9e-02       1.9e-02 <td< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></td<>													
Normal	6 2e-05	5.5e-03			2 1e-08	7 1e-05	5.0e-07	7 6e-03	6.6e-12	2.3e-04		9 0e-06	6 9e-11
122-01       1.66-02       4.10-03       4.30-02       4.60-02       7.00-04       4.30-02       2.40-05       4.90-02       4.90-04       4.30-02       4.90-02       4.90-04       4.30-02       4.90-02       4.90-04       4.30-02       4.90-02       4.90-04       4.30-02       4.90-02       4.90-04       4.30-02       4.90-02       4.90-04       4.30-02       4.90-02       4.90-04       4.30-04       4.90-02       4.90-04       4.30-04       4.90-02       4.90-04       4.30-04       4.90-02       4.90-04       4.30-04       4.90-02       4.90-04       4.30-02       4.90-02       4.90-04       4.30-04       4.90-02       4.90-04       4.30-02       4.90-02       4.90-04										_		2.00-14	1.70-08
2.22010       9.60-05       1.30-03       2.00-02       7.60-02       7.60-03       1.90-04       8.40-04       3.40-02       4.10-03         6.10-08       5.20-10       9.60-05       1.30-03       2.00-03       7.60-02       7.60-02       1.30-01       4.90-04       8.40-04       3.40-02       4.10-03         8.00-11       1.20-11       5.20-08       8.10-08       1.20-11       2.70-07       2.80-09       5.60-05       1.80-04       3.50-08       1.80-04         8.00-11       1.20-11       5.20-08       6.10-08       1.20-11       8.00-08       2.00-09       5.60-05       1.80-08       3.50-08       1.80-04         3.00-03       3.60-04       7.60-02       1.90-01       4.80-24       3.30-03       3.50-08       1.80-04       1.80-04       1.90-02       1.90-01       4.40-02       1.90-02       1.90-01       4.40-02       1.90-02       1.90-01       4.40-02       1.90-01       2.60-07       5.60-08       6.60-16       1.20-07       6.60-16       1.20-07       6.60-16       1.20-07       6.10-15       7.20-13       9.40-04       1.40-02       2.60-07       5.60-08       6.60-16       1.20-07       6.10-15       7.20-13       9.20-93       1.60-15       2.60-07       5.60-16					1.00 00						6 00 02	2.00 14	4.9= 06
3.9e-03       1.2e-06       9.0e-03       1.2e-05       2.9e-03       1.2e-06       1.2e-06       1.2e-06       1.2e-06       1.2e-04       3.4e-04       3.4e-04       3.4e-04       3.4e-04       3.4e-04       3.4e-04       4.4e-04       3.4e-04       3.4e-03					2.00.02						0.96-02	2.46-00	4.10.03
6.16-03         5.2e-10         1.3e-03         6.3e-04         1.0e-03         3.7e-04         3.7e-05         5.3e-05         3.5e-04         1.3e-04         3.7e-04         3.7e-05         5.3e-05         3.5e-04         1.3e-04         3.7e-04         3.7e-05         5.3e-05         3.5e-04         3.5e-04         3.7e-05         2.0e-05         5.6e-05         2.0e-05         5.6e-05         2.0e-05         5.6e-05         3.3e-04         3.3e-04         3.3e-04         3.3e-04         3.3e-04         3.3e-04         3.3e-04         3.3e-04         3.3e-05         3.3e-05 <t< td=""><td></td><td></td><td>9.06-09</td><td></td><td></td><td></td><td>7.56-05</td><td></td><td>4.98-04</td><td></td><td></td><td>3.40-02</td><td>4.16-03</td></t<>			9.06-09				7.56-05		4.98-04			3.40-02	4.16-03
810-11       1.2e-11       5.2e-08       8.1e-08       1.2e-11       5.2e-08       3.6e-08       1.2e-11       8.0e-08       2.0e-09       5.6e-05       1.8e-08       3.3e-08								3.7e-07				3.56-08	1.8e-04
3 1e-24       1.2e-23       1.1e-17       2.2e-26       1.1e-28       7.6e-02       1.9e-01       4.3e-04       4.4e-02       1.9e-01       7.6e-02       1.9e-01       4.3e-04       4.4e-02       1.9e-02       7.6e-03	8.0e-11	1.2e-11		8.1e-08		2.7e-11						1.8e-08	3.3e-06
3.1e-24       1.2e-23       1.1e-17       2.2e-26       1.1e-28       7.3e-22       1.7e-18       4.8e-24       3.3e-20       7.8e-21       1.6e-19       5.3e-25       7.5e-23         1.4e-02       7.6e-08       2.3e-07       8.0e-06       1.3e-02       1.0e-01       9.2e-03       1.1e-07       9.4e-04       2.5e-07       2.5e-07         1.3e-10       5.5e-08       6.9e-12       8.3e-10       1.8e-02       9.5e-08       6.6e-16       1.2e-07       6.1e-15       7.2e-13         9.3e-16       2.8e-15       6.5e-20       6.9e-18       5.2e-16       1.4e-13       1.7e-12       6.3e-10       1.8e-21       1.4e-09       2.8e-20       2.4e-17         9.9e-03       2.5e-01       3.2e-09       5.1e-06       4.3e-06       2.1e-04       8.2e-06       4.2e-04       1.5e-08       1.1e-02       4.8e-03       7.0e-02       1.4e-07         9.9e-03       2.5e-01       3.2e-09       5.1e-06       4.3e-06       2.1e-04       8.2e-06       4.2e-04       1.5e-08       1.1e-02       4.8e-03       7.0e-02       1.4e-07         9.9e       9.9e<			0.00 00		0.00 01							1.9e-02	
14e-02       7.6e-08       2.3e-07       8.0e-06       1.3e-02       1.0e-01       9.2e-03       1.1e-07       9.4e-04       2.5e-07         1.3e-10       5.5e-08       6.9e-12       8.3e-07       8.0e-06       6.2e-07       9.5e-08       6.6e-16       1.2e-07       1.4e-09       6.1e-15       7.2e-13         9.3e-16       2.5e-07       6.3e-16       1.4e-13       1.7e-12       6.3e-10       1.8e-21       3.6e-20       1.4e-09       2.6e-07       2.4e-17         9.9e-03       2.5e-01       3.2e-09       5.1e-16       4.3e-06       2.1e-04       4.2e-04       1.5e-08       1.4e-09       2.6e-20       1.4e-03       7.0e-02       1.4e-07         9.9e-03       2.5e-01       3.2e-09       5.1e-16       4.3e-06       2.1e-04       4.2e-04       1.5e-08       1.1e-02       4.8e-03       7.0e-02       1.4e-07         9.9e-03       2.5e-01       3.2e-09       5.1e-16       4.2e-04       1.5e-08       1.1e-02       4.8e-03       7.0e-02       1.4e-07         9.9e-11		1.2e-23				_					1.6e-19	5.3e-25	7.5e-23
13e-10       5.5e-08       6.9e-12       8.3e-10       4.9e-08       6.3e-05       4.2e-07       9.5e-08       6.6e-16       1.2e-07       6.1e-15       7.2e-13         9.3e-16       2.8e-15       6.5e-20       6.9e-18       5.2e-61       1.4e-13       1.7e-12       6.3e-10       1.8e-21       1.4e-03       2.6e-20       2.4e-17         9.9e-03       2.5e-01       3.2e-09       5.1e-06       4.3e-06       2.1e-04       8.2e-06       4.2e-04       1.5e-08       1.1e-02       4.8e-03       7.0e-02       1.4e-07         V </td <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>1.0e-01</td> <td>9.2e-03</td> <td>1.1e-07</td> <td>9.4e-04</td> <td></td> <td></td> <td>2.5e-07</td>							1.0e-01	9.2e-03	1.1e-07	9.4e-04			2.5e-07
9.3e-16       2.8e-15       6.5e-20       6.9e-18       5.2e-16       1.4e-13       1.7e-12       6.3e-10       1.8e-21       3.5e-20       1.4e-09       2.8e-20       2.4e-17         9.9e-03       2.5e-01       3.2e-09       5.1e-06       4.3e-06       2.1e-04       8.2e-06       4.2e-04       1.5e-08       1.1e-02       4.8e-03       7.0e-02       1.4e-07         Y<	1.3e-10	5.5e-08	6.9e-12	8.3e-10	4.9e-08	6.3e-05	4.2e-07	9.5e-08	6.6e-16	1.2e-07		6.1e-15	7.2e-13
9.9e-03 2.5e-01 3.2e-09 5.1e-06 4.3e-06 2.1e-04 8.2e-06 4.2e-04 1.5e-08 1.1e-02 4.8e-03 7.0e-02 1.4e-07 V V V V V V V V V V V V V V V V V V V	9.3e-16	2.8e-15	6.5e-20	6.9e-18	5.2e-16	1.4e-13	1.7e-12	6.3e-10	1.8e-21	3.6e-20	1.4e-09	2.8e-20	2.4e-17
BLCA BRCA COAD LGG HNSC KRC LUAD LUSC RAD SKCM SKCM STAD STAD	9.9e-03	2.5e-01	3.2e-09	5.1e-06	4.3e-06	2.1e-04	8.2e-06	4.2e-04	1.5e-08	1.1e-02	4.8e-03	7.0e-02	1.4e-07
BLCA BRCA COAL COAL LUAC LUAC LUAC LUAC RACM SKCM UCEC	-	-	-	(0	~	~	~	~	-	-	~	-	0
⊞ ₩ 8 - ₹ ₹ 1 - 1 ₩ % № 4 - 8	ð	ð	AD	0	SC	RC	IAD	SC	SAD S	S	AC AC	¶ 2	ы Ш
	B	н	8		£	×	1	1	Ľ.	š	S	É	S

-----

#### 839 Fig 2a



- 0---

- 0-10

- 851 Fig 2b

1.1e-21	8.2e-31	3.3e-19	3.5e-21	1.9e-30	2.5e-30	9.8e-29	1.3e-12	2.8e-19	2.9e-13	8.4e-19	2.3e-32	1.8e-34
8.9e-19	1.0e-20	2.7e-10	8.1e-12	3.4e-12	2.2e-17	1.8e-14	7.2e-05	1.4e-12	4.9e-10	1.1e-21	1.4e-13	7.9e-19
1.4e-13	2.4e-27	2.9e-16	3.8e-15	1.4e-33	4.4e-23	7.4e-16	9.5e-15	4.0e-19	7.6e-06	1.8e-22	8.5e-23	1.4e-24
.9e-02	1.7e-04	2.6e-02	1.4e-08	7.6e-06	8.6e-07	7.9e-03		3.3e-02		3.1e-03	2.7e-04	6.4e-03
.1e-16	6.8e-14	1.5e-07	2.0e-16	4.2e-16	1.0e-11	1.0e-10		7.3e-09	2.6e-04	7.8e-06	1.5e-14	3.2e-14
.7e-12	5.2e-10	3.5e-11	6.7e-10	1.4e-13	1.3e-12	3.1e-07	2.0e-02	1.8e-07	4.7e-06	4.3e-13	1.4e-13	5.8e-13
		1.4e-02										1.8e-34 7.9e-19 1.4e-24 6.4e-03 3.2e-14 5.8e-13 1.4e-05 5.9e-02 6.7e-08 2.4e-07 6.0e-17
6e-04	5.6e-05	3.1e-04	2.8e-10	1.9e-05	4.5e-08	3.8e-06		2.7e-04		9.2e-06	3.0e-06	1.4e-05 5.9e-02 6.7e-08 2.4e-07 6.0e-17 6.2e-08
			2.1e-01	1.3e-02	1.8e-01	3.5e-02			4.8e-04	1.1e-01	2.4e-04	5.9e-02
.8e-04	3.2e-06	8.1e-03	1.2e-07	9.6e-03	1.0e-08	3.9e-05		2.1e-04	2.3e-02	1.5e-10	4.6e-05	6.7e-08
	6.3e-03		4.2e-05		3.5e-05			2.0e-01		1.6e-03		
.2e-05	1.2e-05	2.4e-04	1.1e-12	2.4e-08	4.7e-10	1.7e-05		1.5e-04		1.4e-08	5.0e-08	2.4e-07
.7e-12	2.2e-08	6.1e-11	2.1e-09	4.8e-14	1.5e-14	3.4e-14		1.7e-06	1.5e-08	6.4e-10	2.6e-15	6.0e-17
.3e-10	8.5e-07	5.2e-04	1.2e-04	5.4e-07	1.8e-03	9.9e-04		1.1e-02	3.8e-06		1.0e-07	6.2e-08
.3e-17	2.7e-18	1.3e-08	8.2e-19	1.8e-19	7.1e-20	4.8e-19	4.0e-08	3.6e-17	2.8e-11	2.8e-23	5.3e-18	1.4e-13
l.3e-11	7.3e-15	2.2e-10	3.2e-18	4.0e-17	6.1e-11	3.3e-12	8.1e-03	9.0e-09	1.6e-07	9.0e-10	1.9e-15	2.1e-18
5.3e-06	1.8e-04				3.1e-02		1.3e-01	2.2e-04	1.7e-03	4.0e-02	1.4e-03	2.4e-07 6.0e-17 6.2e-08 1.4e-13 2.1e-18 4.9e-04 1.9e-12 7.6e-04 1.9e-15 6.2e-08 3.6e-07 9.4e-03 5.3e-03 1.5e-06
6.4e-17	1.1e-15	2.8e-05	2.0e-11	3.6e-12	1.4e-13	5.8e-13	4.9e-07	2.8e-12	8.9e-07	4.4e-17	6.8e-19	1.9e-12
			1.1e-02	1.0e-02				5.4e-02		1.0e-01		
6.7e-02			2.5e-04	2.7e-02	4.4e-02	1.5e-01		4.1e-03		6.0e-02	3.4e-06	7.6e-04
2.7e-10	5.7e-11	3.6e-08	2.6e-15	7.2e-13	1.5e-09	5.9e-11		4.9e-10	1.4e-04	1.6e-11	9.8e-11	1.9e-15
6.6e-06	8.7e-09	3.7e-06	2.8e-05	9.6e-04	5.7e-09	1.8e-06	1.1e-02		3.7e-03	5.5e-06	6.9e-09	6.2e-08
9.9e-06	2.5e-07		5.1e-06	1.9e-04	3.5e-04	1.8e-06		2.5e-05	1.6e-03	1.2e-08	1.0e-02	3.6e-07
3.4e-03	9.7e-04	7.6e-02	4.0e-04	5.0e-03	3.2e-04			1.3e-01	5.6e-03	2.1e-02	1.1e-02	9.4e-03
1.2e-01	2.9e-03		2.2e-06	3.7e-07	7.2e-05	1.0e-02		1.1e-06		2.4e-01	1.0e-02	5.3e-03
3.2e-04	2.0e-06	4.3e-08	5.1e-03	4.0e-07	8.8e-04	5.7e-02		4.3e-02	3.4e-05	6.6e-03	1.0e-03	1.5e-06
1.2e-02	3.4e-05	3.6e-06	1.1e-01	7.3e-04	8.9e-06	6.4e-02	6.0e-02		3.6e-05	8.5e-05	1.7e-03	2.2e-05
1.4e-03	8.5e-05	3.3e-07	2.2e-05	7.7e-04	2.5e-06	7.6e-05	4.7e-02	6.2e-02	1.1e-01	3.0e-05	4.3e-08	1.6e-05
9.2e-02		7.5e-02		2.5e-01	5.2e-04					1.9e-02	2.1e-01	1.9e-01
5.2e-02				1.0e-01					3.2e-03		1.4e-02	
4.4e-04	6.8e-08		3.9e-07	1.5e-09	3.1e-05	9.8e-03		1.1e-08	3.7e-03	5.3e-06	4.4e-02	5.7e-04
2.8e-04	4.6e-07	2.0e-05	3.4e-07	1.3e-11	2.8e-05	1.5e-02		2.8e-03	9.4e-03	3.4e-03	1.9e-07	1.9e-04
1.3e-02	7.7e-03	2.2e-01		1.1e-03	5.5e-03	2.7e-04	1.4e-03	4.6e-03		7.6e-02	5.9e-02	3.6e-07 9.4e-03 5.3e-03 1.5e-06 2.2e-05 1.6e-05 1.9e-01 5.7e-04 1.9e-04 2.2e-04 3.6e-03 1.5e-06
1.3e-01	5.7e-06	2.4e-03	9.0e-02	1.4e-03		1.7e-01		1.3e-01	6.5e-04		8.7e-03	3.6e-03
6.8e-11	2.0e-06	2.2e-02	1.3e-07	6.9e-03	7.2e-07	2.7e-03		3.6e-04		2.9e-02	3.7e-05	5.3e-03 1.5e-06 2.2e-05 1.6e-05 1.9e-01 5.7e-04 1.9e-04 2.2e-04 3.6e-03 1.5e-06 1.5e-04
1.2e-01			8.9e-02			1.0e-02				2.0e-02	2.4e-04	
1.3e-02	8.0e-02	1.8e-03	8.9e-02	4.8e-03	2.9e-02	7.9e-02			4.9e-02	5.4e-04	8.2e-04	1.5e-04
6.7e-02	3.1e-02	3.5e-02			4.6e-02					6.1e-02		
7.7e-02	6.9e-04	4.8e-05	5.2e-02	1.6e-04	1.2e-02			7.6e-02	1.7e-01	2.5e-04	1.1e-03	2.3e-02
3.2e-05	3.5e-02	5.0e-02	4.3e-08	3.6e-05	1.9e-04	1.1e-04	1.6e-01	2.2e-06	7.9e-02	6.7e-08	2.0e-09	1.9e-03
5.0e-15	1.4e-09	7.0e-11	1.4e-13	3.3e-12	7.3e-11	4.2e-15		1.1e-05	5.8e-09	3.4e-07	6.2e-20	3.6e-19
	1.4e-01	1.4e-03		7.5e-04	1.4e-01							5.1e-04
	5.5e-02	1.6e-02		1.0e-01	6.7e-03			2.0e-02	6.6e-03	9.6e-03	8.2e-04	1.7e-02
		2.0e-05									9.4e-02	2.8e-02
					4.2e-02						4.8e-02	
	-	0	~		(1)	0		0	-	0	1	1.9e-01 5.7e-04 1.9e-04 2.2e-04 3.6e-03 1.5e-04 2.3e-02 1.9e-03 3.6e-19 5.1e-04 1.7e-02 2.8e-02
BLCA	BRCA	COAD	HNSC	KIRC	LGG	LUAD	LUSC	PRAD	SKCM	STAD	THCA	ğ
Β	B	ö	Ŧ	x	_	L	L	Ч	Ś	S.	È	ň

- \_ \_ \_

# 861 Fig 3a

