NK Vue® test

For Natural Killer Cell Activity Determination

Characteristics & Recommendations for Use

JANUARY 2021

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What does the NK Vue test do?

- The NK Vue test for NK cell activity (NKA) measures the amount of interferon-gamma (IFN-ɣ, a cytokine) that is released by NK cells when they are activated.
- The test has two components, the NK Vue tubes and the NK Vue ELISA kit. The tubes contain a proprietary cocktail of cytokines that will specifically activate all NK cells in fresh blood. In doing so, they will release IFN-ɣ into the plasma, which will be quantified by the ELISA assay (expressed in pg of IFN-ɣ per mL of plasma).
- The amount of IFN-ɣ that is being released by the activated NK cells, i.e., the *NK Vue value*, is directly correlated with their capacity to engage other immune cells, triggering an effective immune response.

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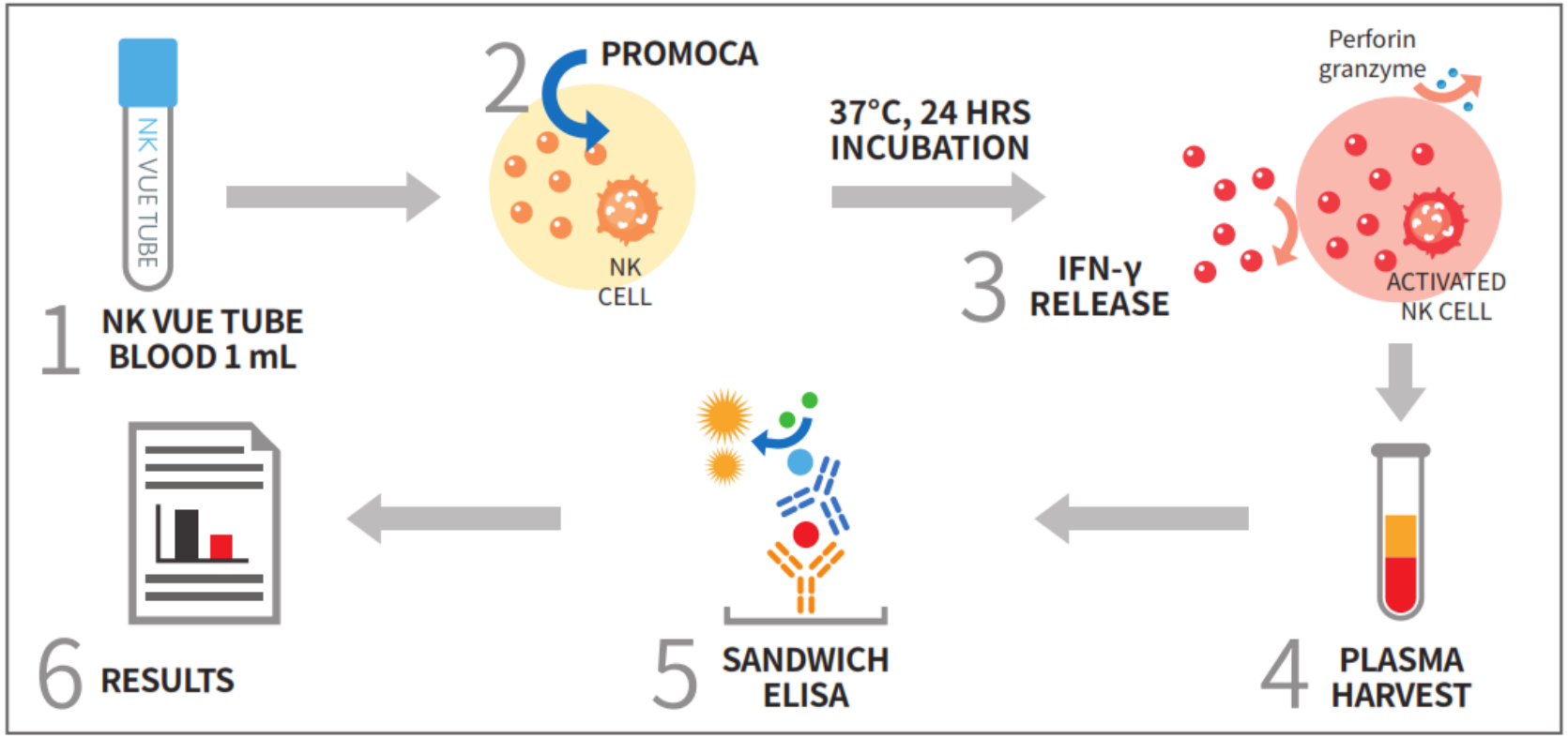
NK Vue is a biomarker assay



Principle of NK VUE

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What is a normal NKA?

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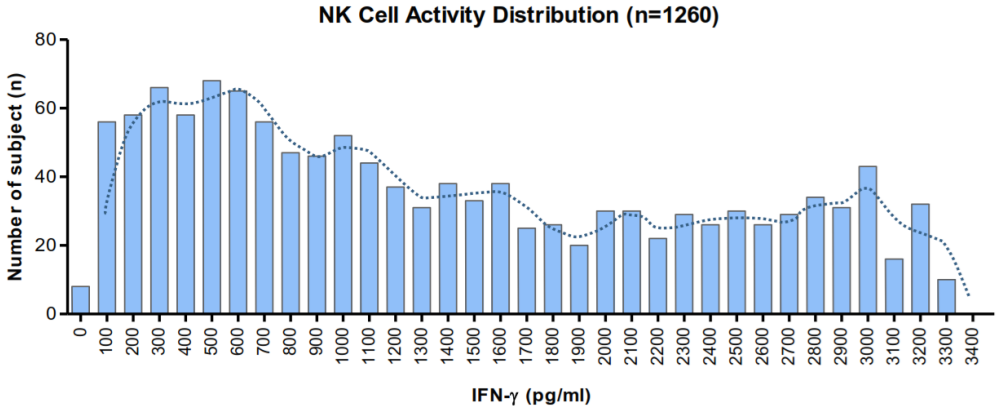
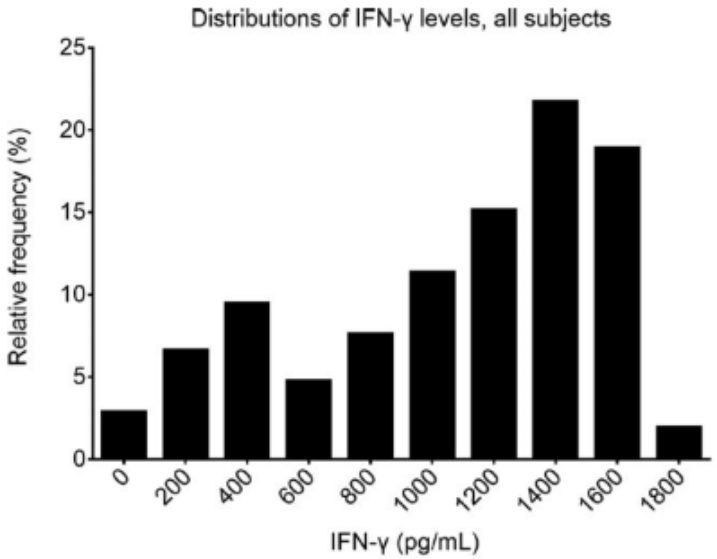
a)

Figure 1. Results of NK Cell Activity



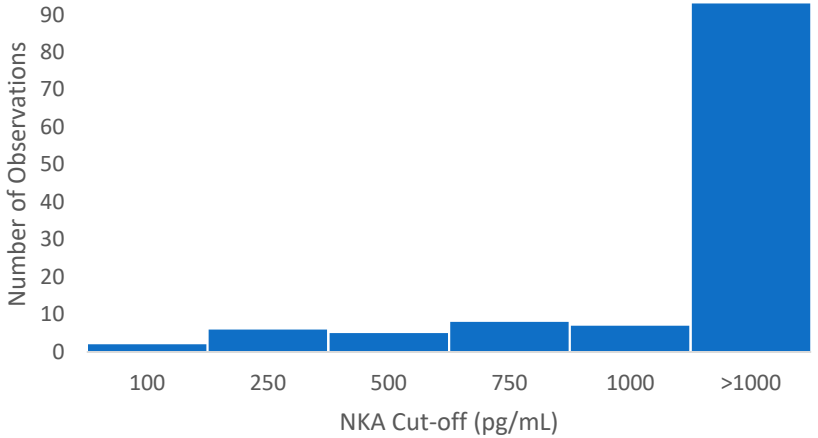
10% of subjects were below 258 pg/mL
N=1260

b)



Less than 10% of subjects had NKA <200 pg/mL
n=106

c)



Less than 7% of subjects had NKA <250 pg/mL
N=121

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a) 2016 KAI-IBS Joint International Conference; November 16(Wed) – 18(Fri), 2016. Sejong University, Seoul, Korea; b) Kim et al, 2018; c) internal data

Why measure NKA?

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Low NK Activity (NKA) is predictive of increased cancer risk

- Epidemiological study on 3,625 individuals (Imai et al., 2000)
- >40 old, followed over a 10 year period
- 154 cancer cases were identified throughout the 10-year long follow-up
- Higher 10 year incidence of cancer in those with lower NKA
- At 10 years, the overall relative risk of cancer was 50% higher in those with low NKA compared to the ones with moderate or high NKA

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Imai et al. (2000). Lancet 356:1795-1799. https://doi.org/10.1016/S0140-6736(00)03231-1.
Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: an 11-year follow-up study of a general population.

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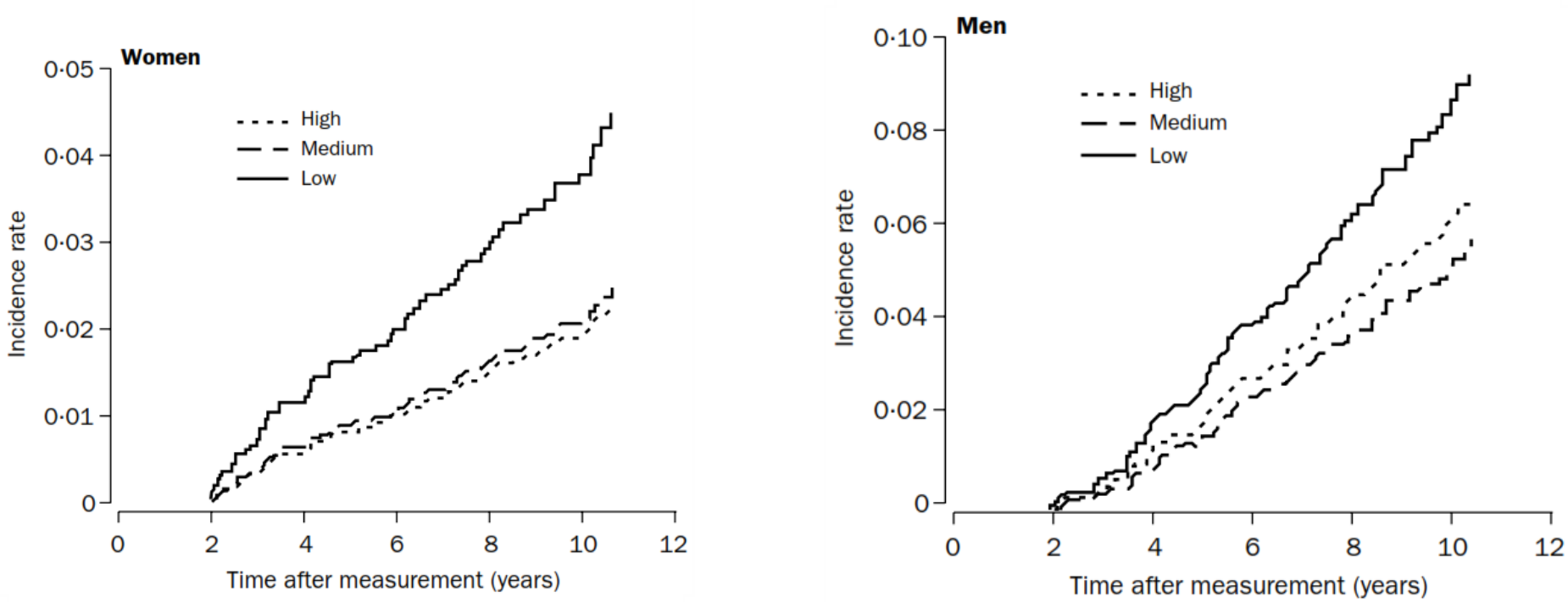
Incidence of cancer based on NKA



Cumulative incidence rates of cancer by cytotoxic activity of peripheral-blood lymphocytes among men and women
Categorised by tertiles. Men—low: ⩽42%; medium: 43–58%; high: >58%. Women—low: 34%; medium: 35–51%; high: >51%.

Imai et al. (2000). Lancet 356:1795-1799. https://doi.org/10.1016/S0140-6736(00)03231-1.
Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: an 11-year follow-up study of a general population.

Relative risk of cancer incidence at year 10 versus baseline levels of NK cell cytotoxic activity (measured with the ^{51}Cr assay)

Cytotoxic Activity (%)	Low	Medium	High
Age-adjusted	1.0	0.59 (0.40–0·87)§	0.63 (0.43–0.92)‡
Lifestyle-adjusted†	1.0	0.60 (0.41–0·87)§	0.64 (0.44–0.94)‡

All data are relative risk (95% CI) analysed using Cox proportional hazard model.
†Adjusted for age at entry, relative body weight, cigarette smoking, alcohol consumption, and intake of green vegetables. ‡$p<0.05$. §$p<0.01$.

- Substantially higher incidence of cancer at year 10 in subjects with low NK cells cytotoxic activity at year 0

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Imai et al. (2000). Lancet 356:1795-1799. https://doi.org/10.1016/S0140-6736(00)03231-1.
Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: an 11-year follow-up study of a general population.

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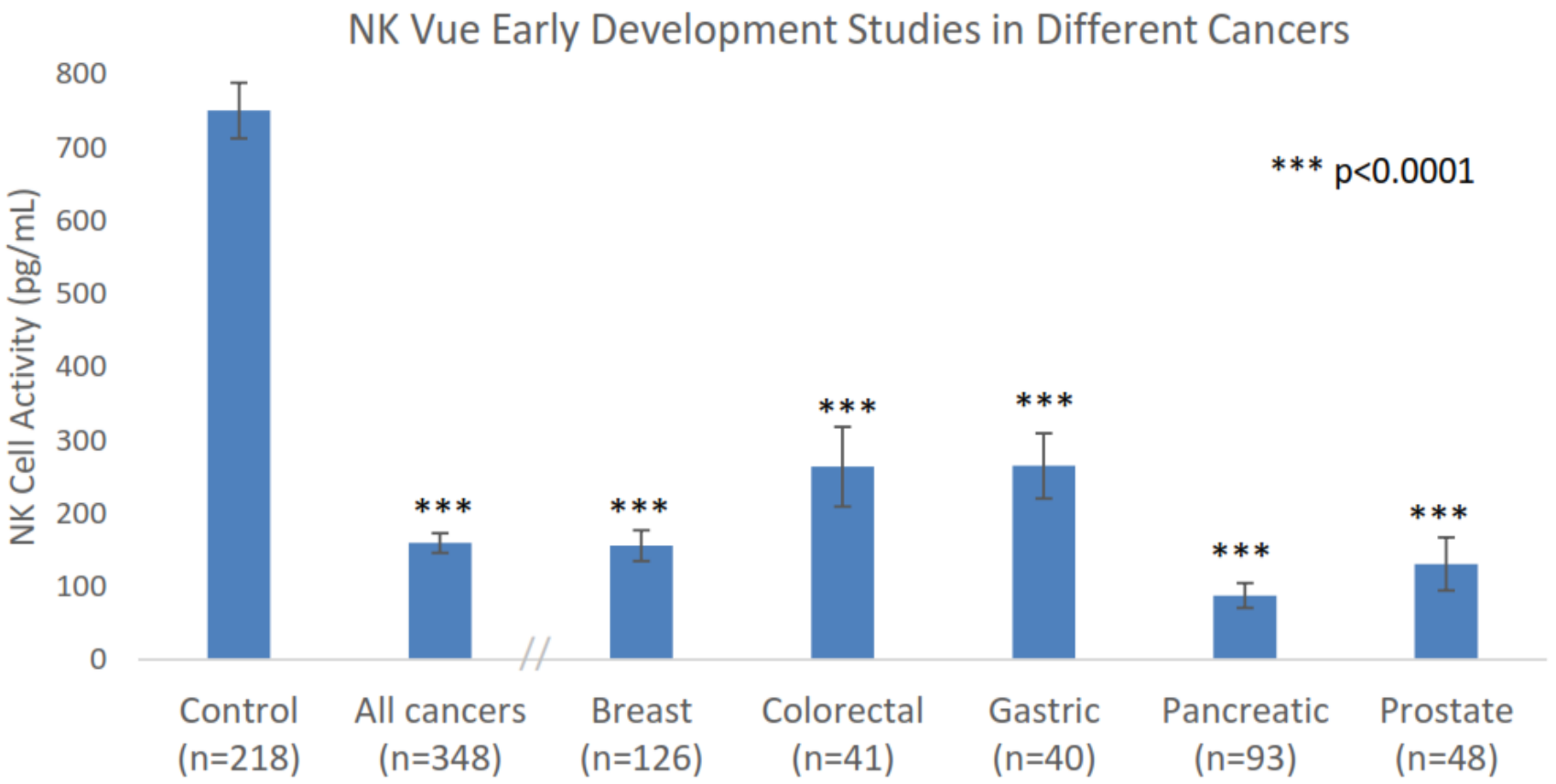
NK cell activity is decreased in cancer - measured with NK Vue



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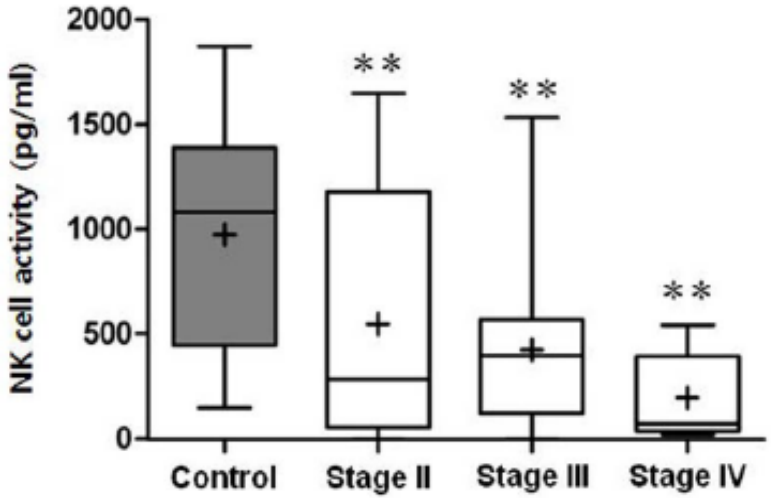
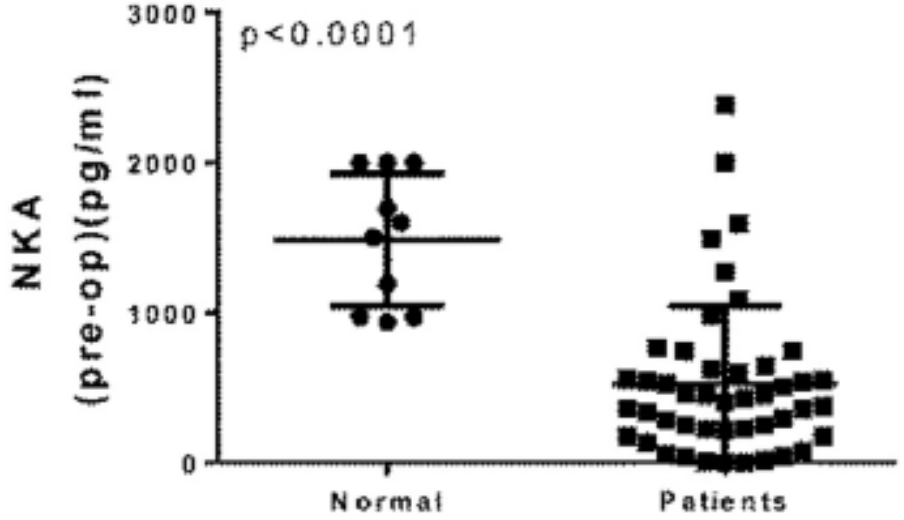
NK cell activity is decreased in prostate cancer



N=51 I----------N=54---------I

(Koo et al., 2013)



(Lu et al., 2020)

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Low NK cell activity predicts prostate cancer

TABLE 4. **NKA IVDD test performance – odds ratio**

Test	Odds ratio	Significant
NKA IVDD (95%CI)	13.33 (2.5-72.3)	Yes
PSA – first value (95%CI)	1.06 (0.9-1.2)	No
PSA – second value (95%CI)	1.29 (1.02-1.6)	Yes

NKA IVDD = natural killer cell activity *in vitro* diagnostic device; PSA = prostate-specific antigen

(Barkin et al., 2017)
N=43

Table 4 - Univariate and multivariate analyses of parameter for predicting prostate cancer.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
PSAD >0.15	0.795 (0.361-1.753)	0.570	1.215 (0.419-3.525)	0.582
FTR <0.10	2.437 (1.085-5.474)	0.031	3.269 (1.058-10.264)	0.040
DRE	10.222 (3.199-32.666)	0.001	12.626 (3.452-46.177)	0.001
NKA <500	5.768 (2.457-13.543)	0.010	7.547 (2.717-20.964)	0.001

PSAD = PSA density (value 0.15<); **FTR** = ratio of total PSA to free PSA (<0.10); **NKA** = Natural killer cell activity

(Tae et al., 2020)
N=102

Table 2
Association between NKA value (as continuous and categorical variables) and prostate cancer or high-grade prostate cancer diagnosis.

	PC vs. no PC		High-grade PC vs. low-grade or no PC	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Univariable models				
NKA value (continuous)**	1.11 (0.99-1.25)	0.069	1.05 (0.95–1.17)	0.358
NKA value (< 200 vs. ≥ 200 pg/mL)	3.59 (1.10-11.6)	0.033	1.63 (0.64–4.10)	0.304
Multivariable models*				
NKA value (continuous)**	1.16 (1.01-1.32)	0.031	1.11 (0.98–1.26)	0.115
NKA value (< 200 vs. ≥ 200 pg/mL)	4.89 (1.34-17.8)	0.016	2.51 (0.85–7.40)	0.095

* Adjusted for age, race, PSA, prostate volume, and DRE findings.
** Modeled per 100 pg/mL decrease in NKA value.

(Vidal et al., 2019)
N=94

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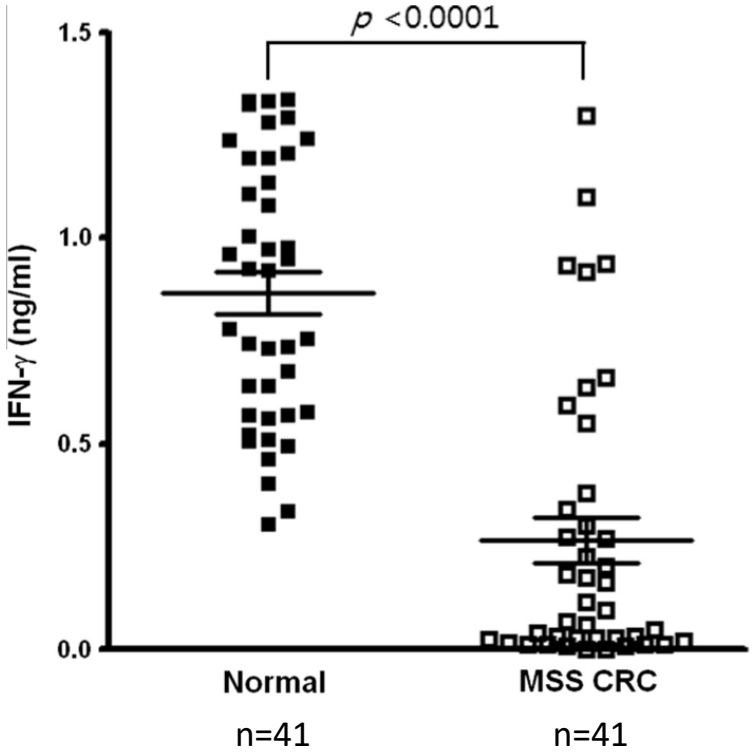
NK cell activity is decreased in CRC



(Lee et al., 2014)

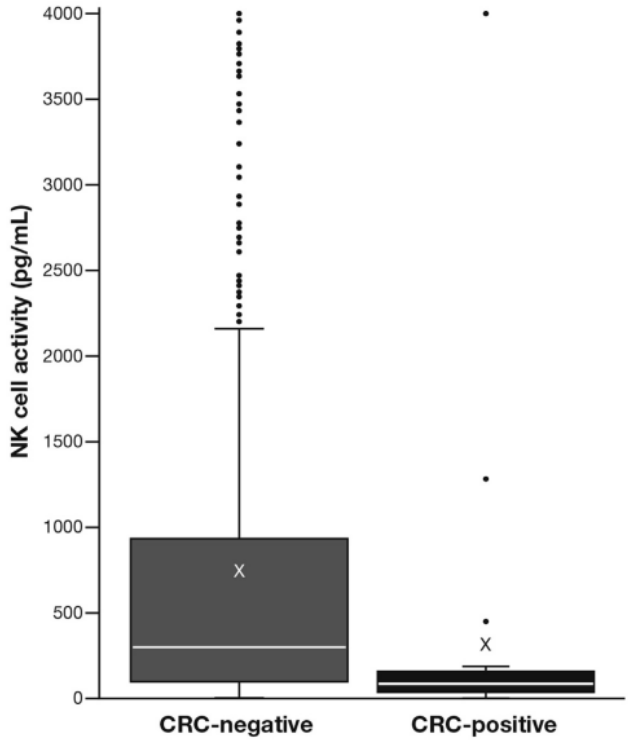


Figure 2. Comparison of the NK cell activities in CRC-negative (n = 849) and pathologically confirmed CRC (CRC positive; n = 23) subjects; *P* = .0002.

(Jobin et al., 2017)

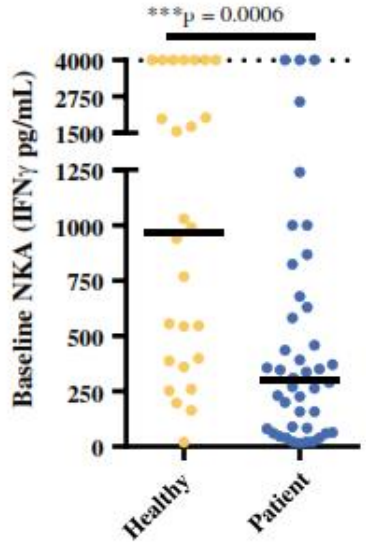


FIG. 1 NK cell IFNγ secretion (NKA) is reduced in CRC patients. NKA from healthy donors (n = 27) and CRC patients (n = 42) before surgery (baseline) was assessed following a 24 h stimulation with Promoca™ cytokine cocktail. Upper limit of detection for the NK Vue™ assay is 4,000 pg/mL. Median indicated by solid line. Mann–Whitney U test

(Angka et al., 2018)

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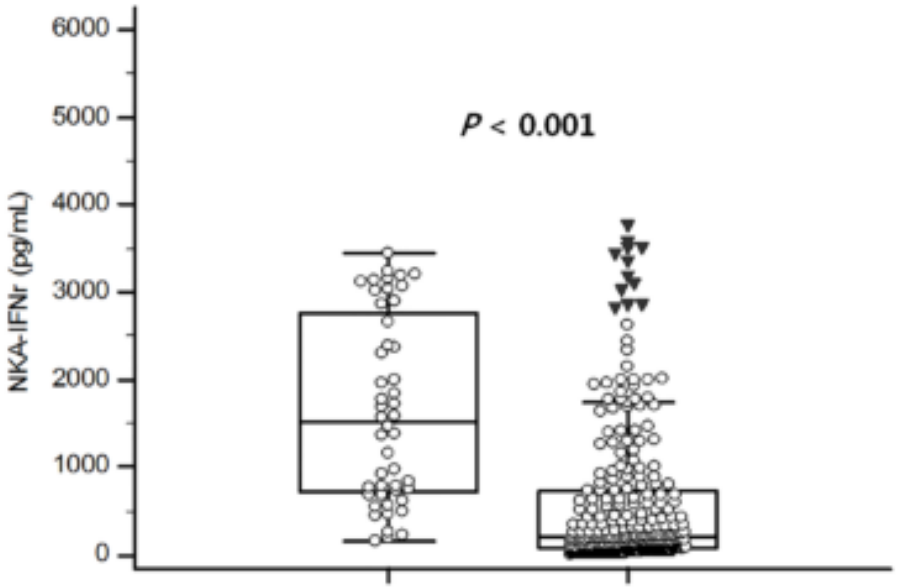
NK cell activity is decreased in Gastric and Lung cancer



n=48 n=261

Gastric cancer
Lee et al, 2017

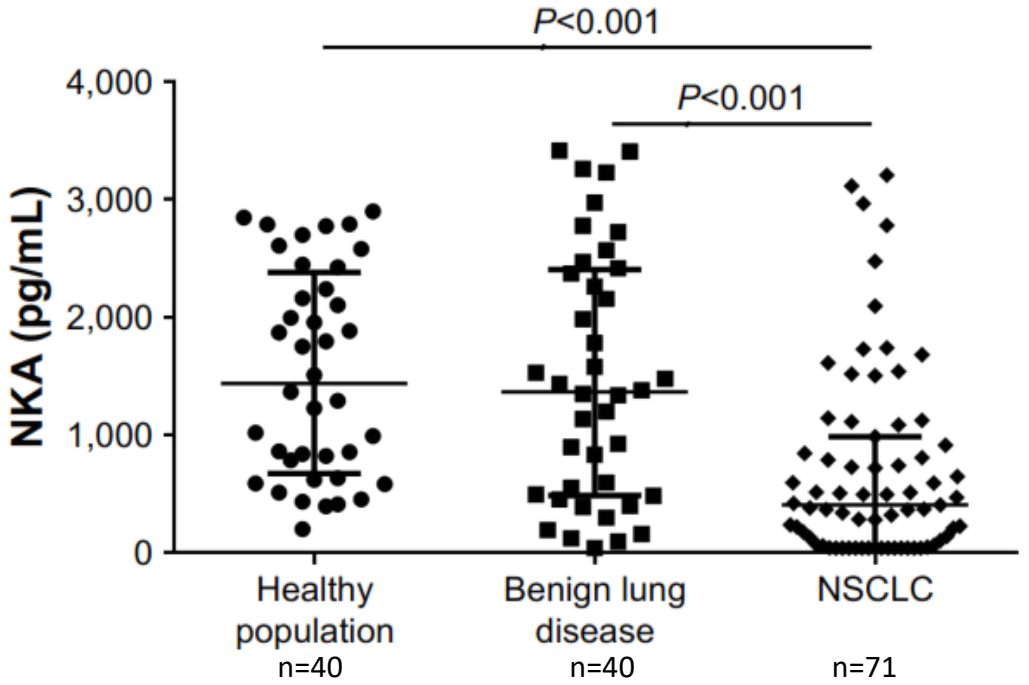


Figure 1 Comparison of NKA in three groups.
Notes: NKA is significantly decreased in NSCLC patients compared with that in healthy population and patients with benign lung disease (both $P<0.001$). Bars denote median and IQR.

Lung cancer
(Choi et al., 2019)

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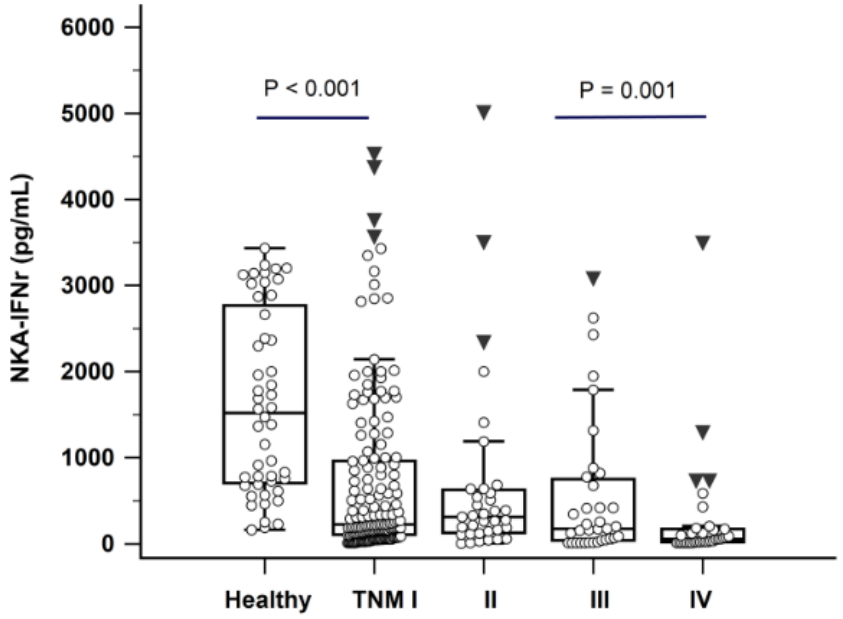
NK cell activity decreases with severity of GC and NSCLC



(Lee et al., 2017)

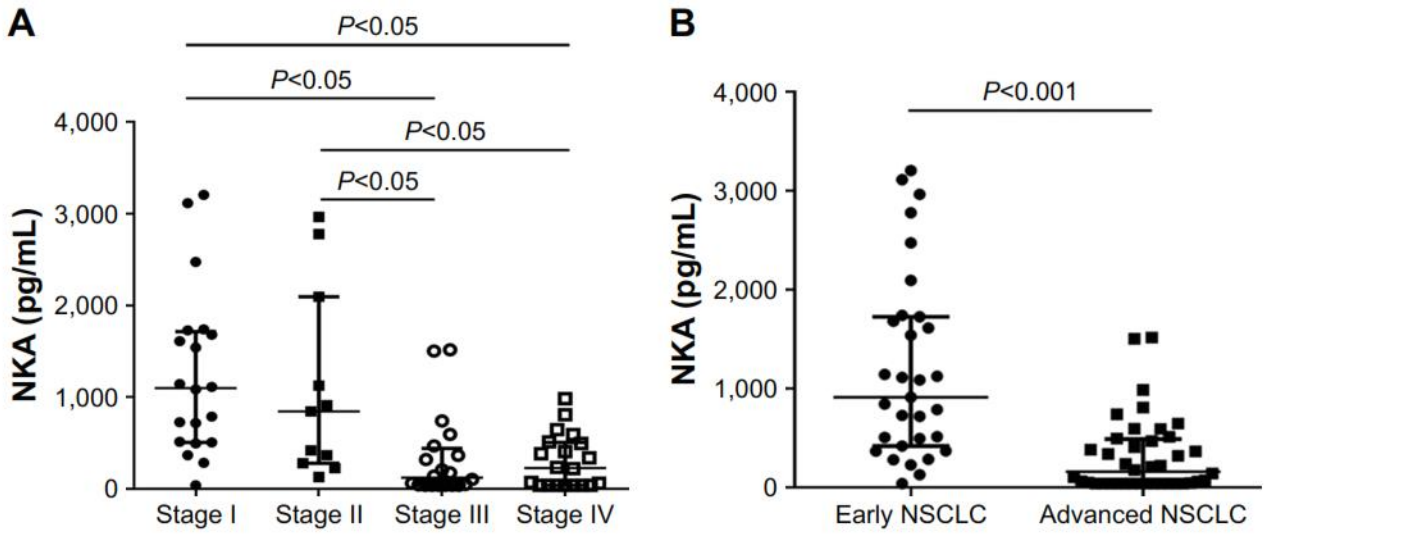


Figure 2 Comparison of NKA according to the stage of NSCLC.
Notes: NKA in stage III or IV was significantly lower than that in stage I or II (all $P<0.05$). There was no significant difference between stage I and II or stage III and IV (**A**). NKA was significantly lower in those with advanced (stage III and IV) NSCLC than in those with early-stage (stage I and II) NSCLC ($P<0.001$) (**B**).
Abbreviations: NKA, natural killer cell activity; NSCLC, non-small cell lung cancer.

(Choi et al., 2019)

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NKA is decreased in hematological cancers

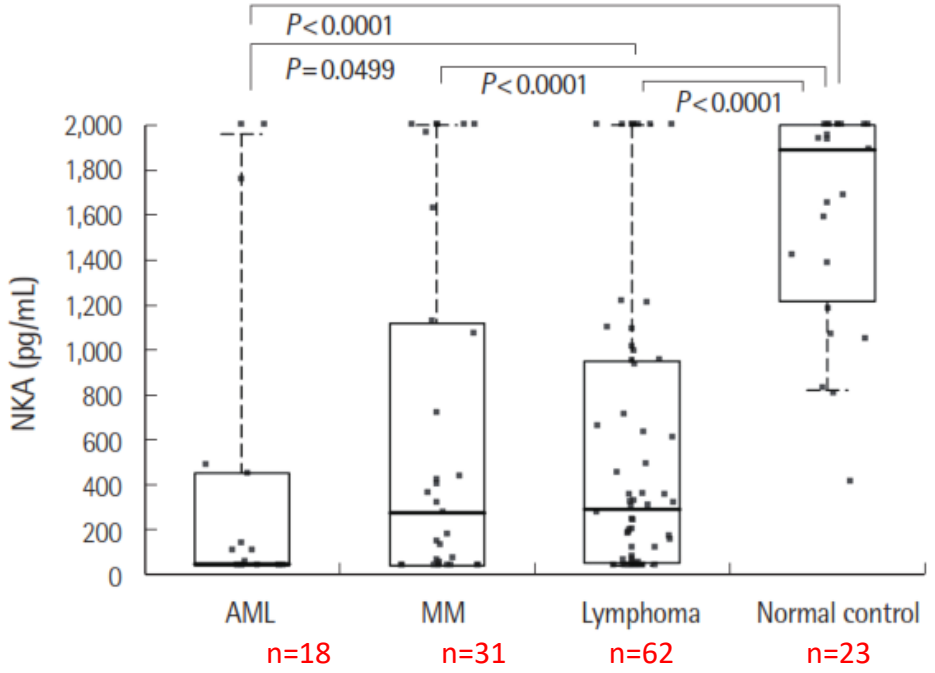

Fig. 1. Comparisons of the natural killer (NK) cell activity (NKA) among patients with hematological malignancies at diagnosis and controls. Boxes are inter-quartile ranges, horizontal bars are medians, and dotted lines are 10th and 90th percentiles.

(Park et al., 2018)

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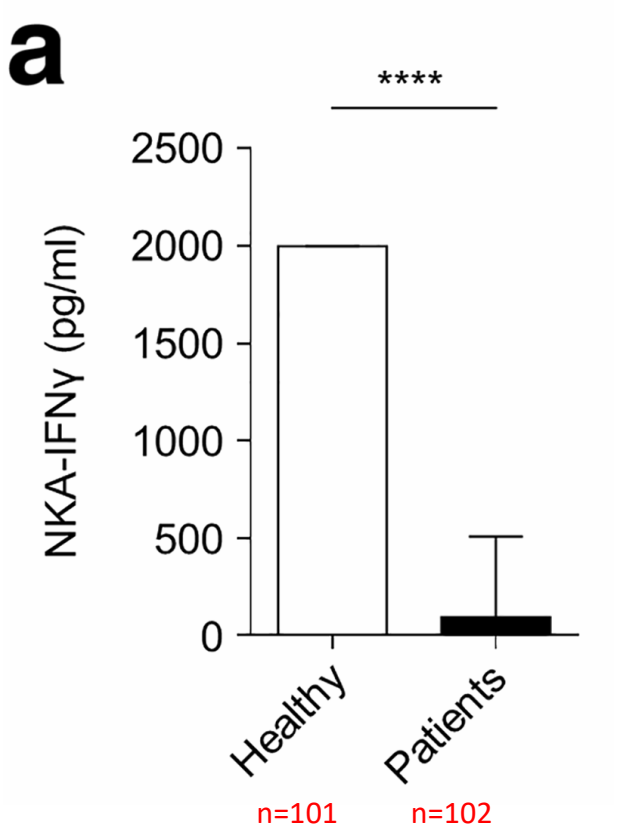
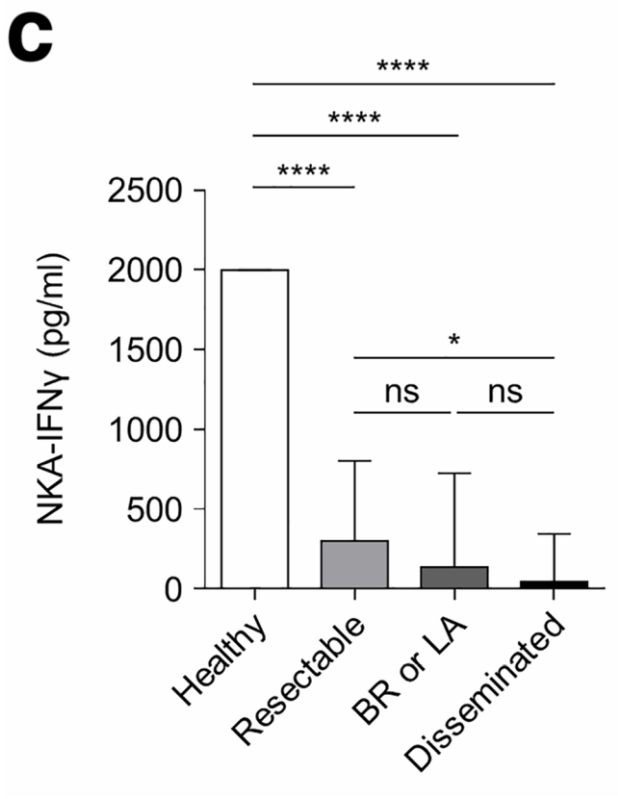
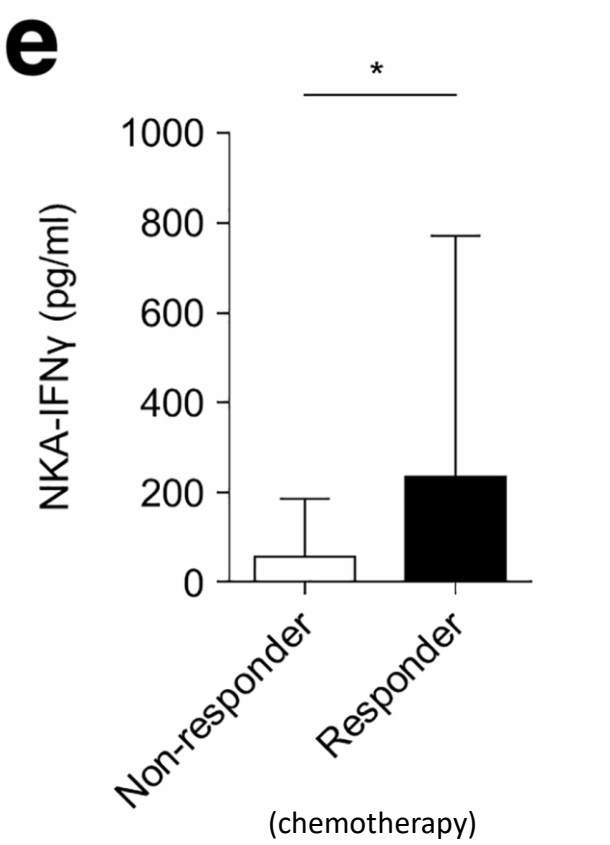
NKA is decreased in pancreatic cancer







(chemotherapy)

(Lee et al., 2020)

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NKA and surgery

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NKA is highly reduced after CRC surgery and could remain low for 28 days

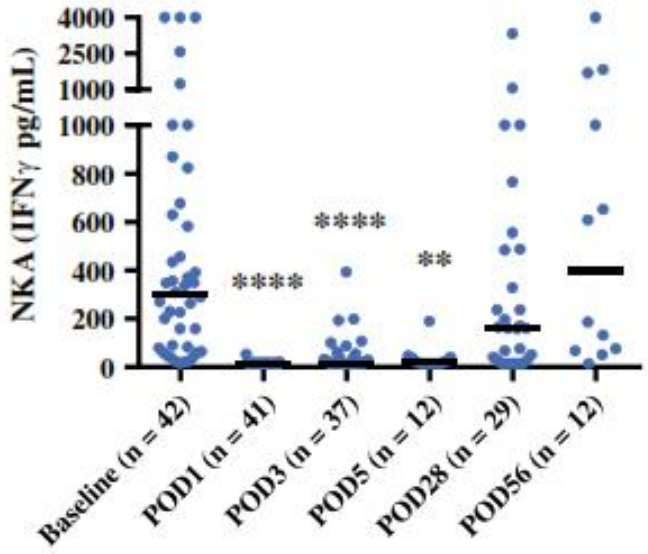
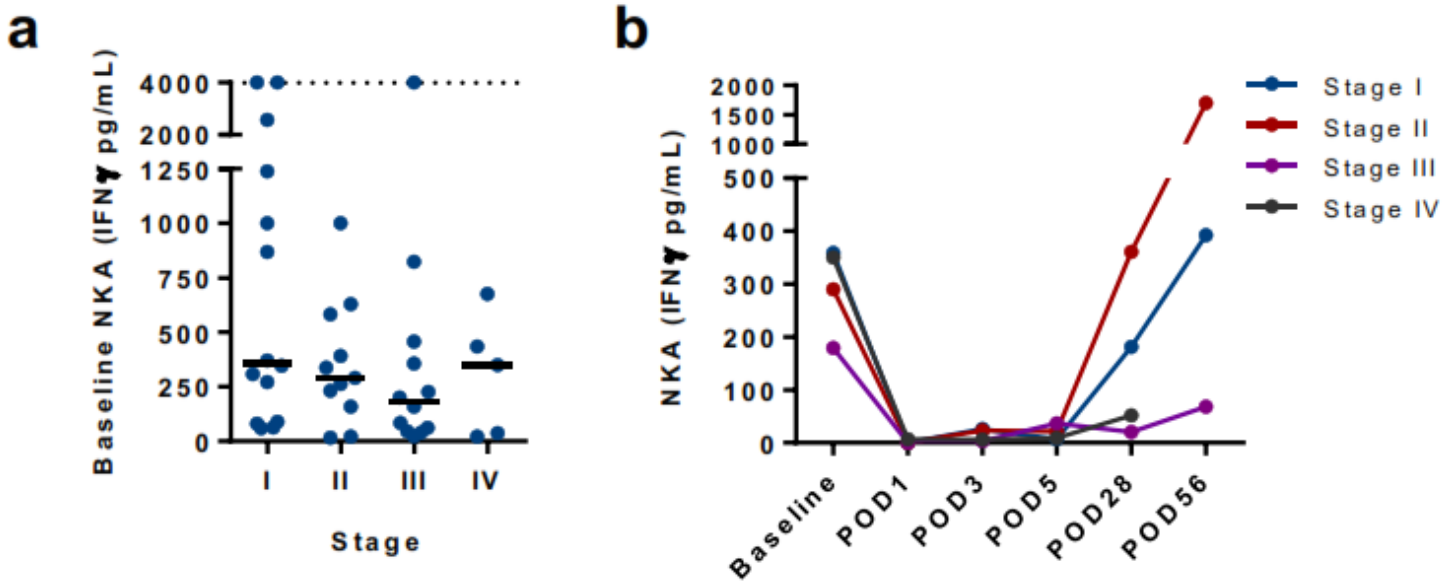


FIG. 2 NK cell IFNγ secretion (NKA) is reduced following surgery. NKA measured in CRC surgery patients on the indicated post-operative days (POD). Solid line indicating the median; Kruskal–Wallis tests (**$p = 0.0035$ and ****$p < 0.0001$)



Supplemental Figure 2. The effect of cancer stage upon NK cell IFNγ secretion (NKA). (a) NKA at baseline; Kruskal-Wallis tests. Median indicated by solid line**. (b)** Median NKA of patients categorized by Stage at Baseline, POD1, 3, 5, 28, and 56.

(Angka et al., 2018)

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NKA and response to chemotherapy in advanced cancer

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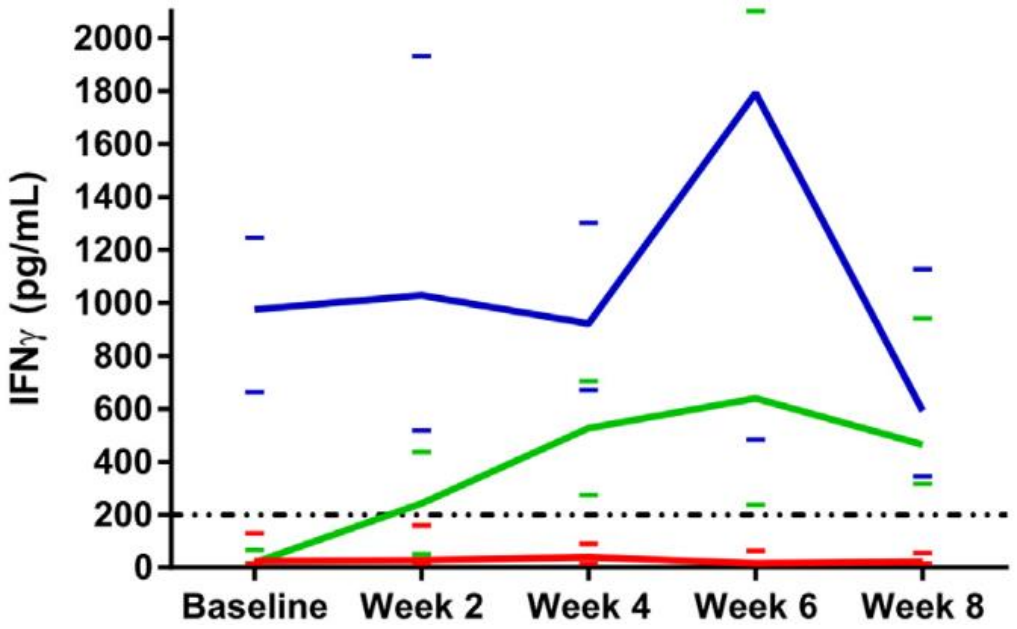
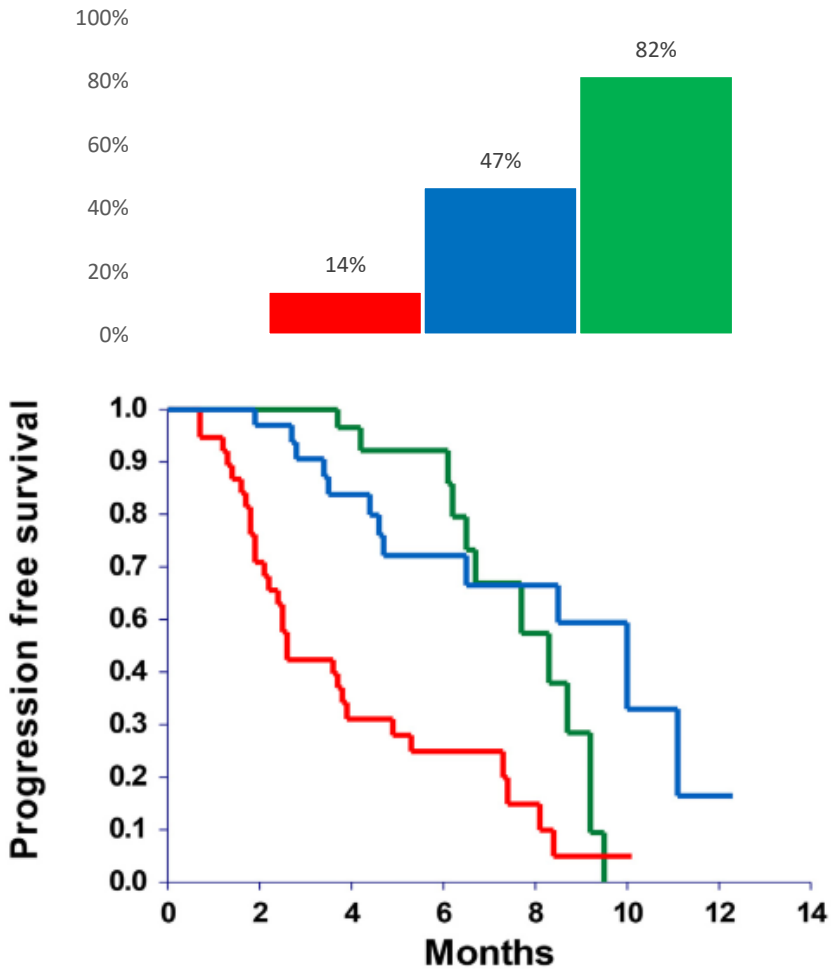
NKA predicts response to therapy in prostate, ovary and CR cancer



(Hansen et al., 2019)
n=93

Response to chemotherapy based on NKA



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Interpretation of NK Vue test results

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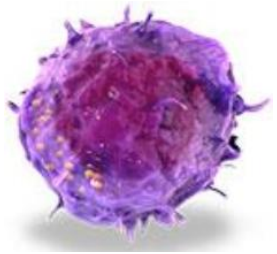

WHAT DO THESE RESULTS MEAN?

Normal (250 pg/ml or greater)	The activity of NK cells is normal or in good condition. The innate immune system's NK cells are working properly.
Borderline (100~249 pg/ml)	The activity of NK cells are below normal values. This could be a sign of a reduction in NK cell activity due to a disease. It could also be caused by temporary physical or psychological stress.
Low (below 100 pg/ml)	The activity of NK cells are very low. This could be due to disease, medication, or psychological stress, as they may reduce NK cell activity.

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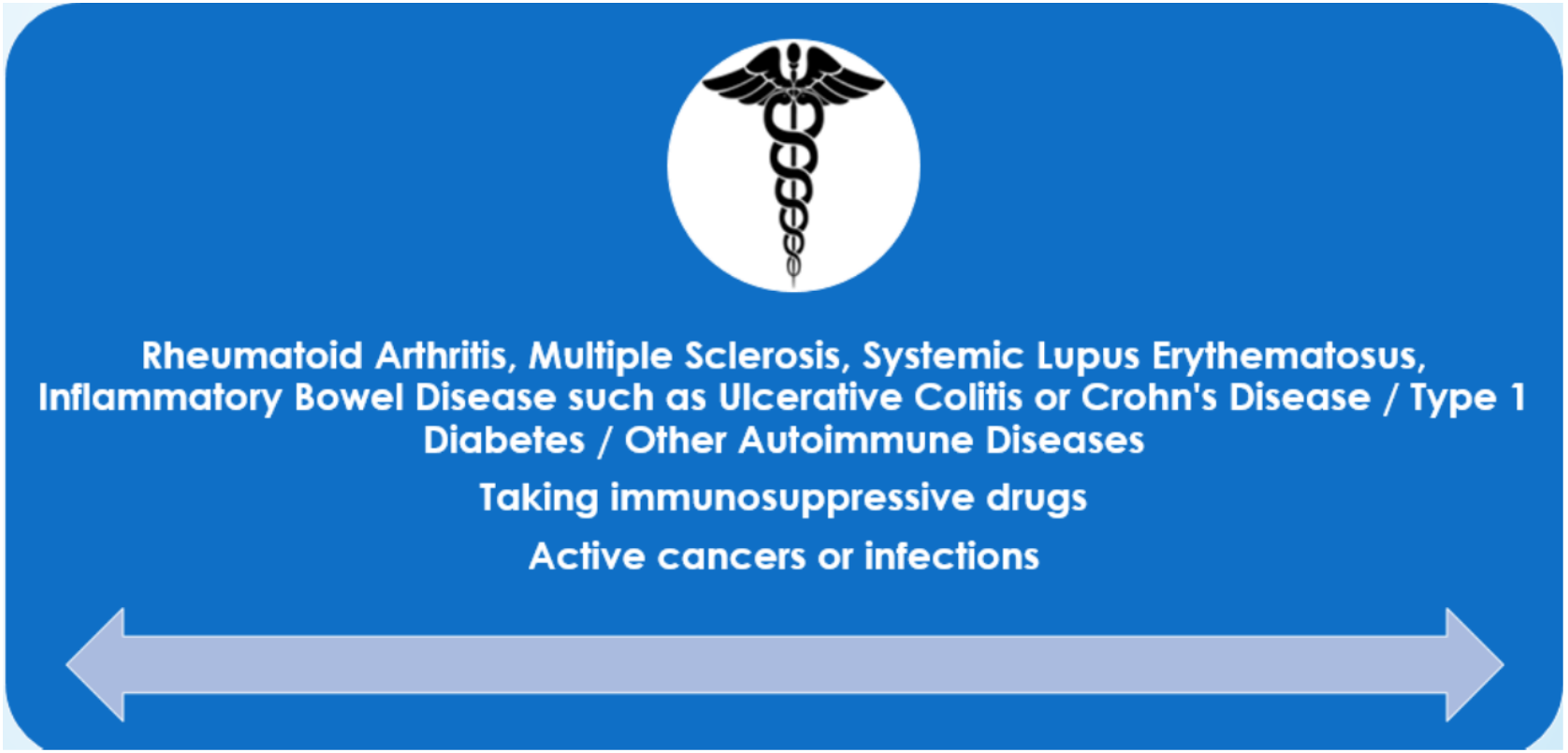
Conditions which may affect NK Vue results

A low NKA may be seen in the following conditions



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Suggestions for low NKA follow-up

NKA <250 pg/mL

Exclude the following conditions:

Rheumatoid Arthritis, Multiple Sclerosis, Systemic Lupus Erythematosus, Inflammatory Bowel Disease such as Ulcerative Colitis or Crohn's Disease / Type 1 Diabetes / Other Autoimmune Diseases

Taking immunosuppressive drugs

Active cancers or infections

Active surveillance for cancer (i.e. suggested cancer screening programs: breast, prostate, cervical)

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Suggestions for low NKA follow-up

Confirm that

- patient does not have any excluding conditions
- patient did not have an infection at time of blood collection

Direct patient to current screening programs

- Colonoscopy
- PSA discussion
- Mammography
- PAP test

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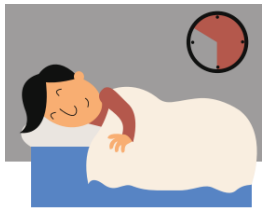
Suggestions for low NKA follow-up

Discuss Lifestyle modifications

- Stress management
- Smoking cessation
- Sleep
- Diet
- Exercise



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Clinical Application for the Use of NK Vue

Risk assessment tool for CRC

- to prioritize colonoscopy waiting lists

- to convince patients to be compliant to their GP's request for a colonoscopy

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