DATACK

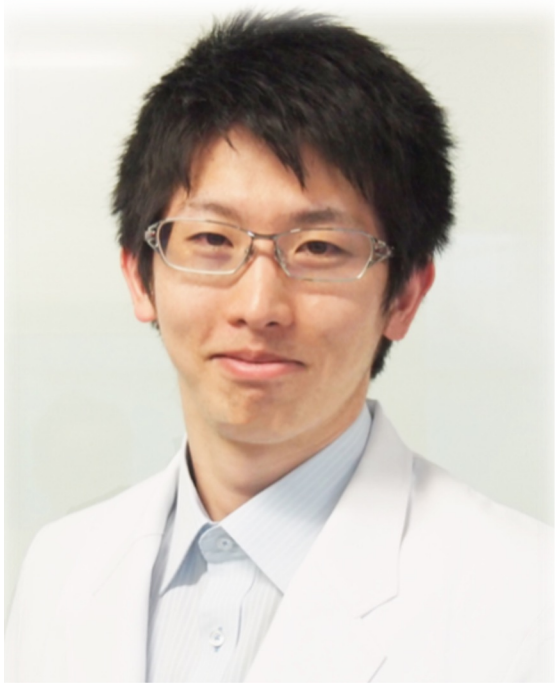
Can Real-world Data Contribute to Medicine?

Datack Inc,
Hideki Ninomiya

Table of Contents

History of Datack

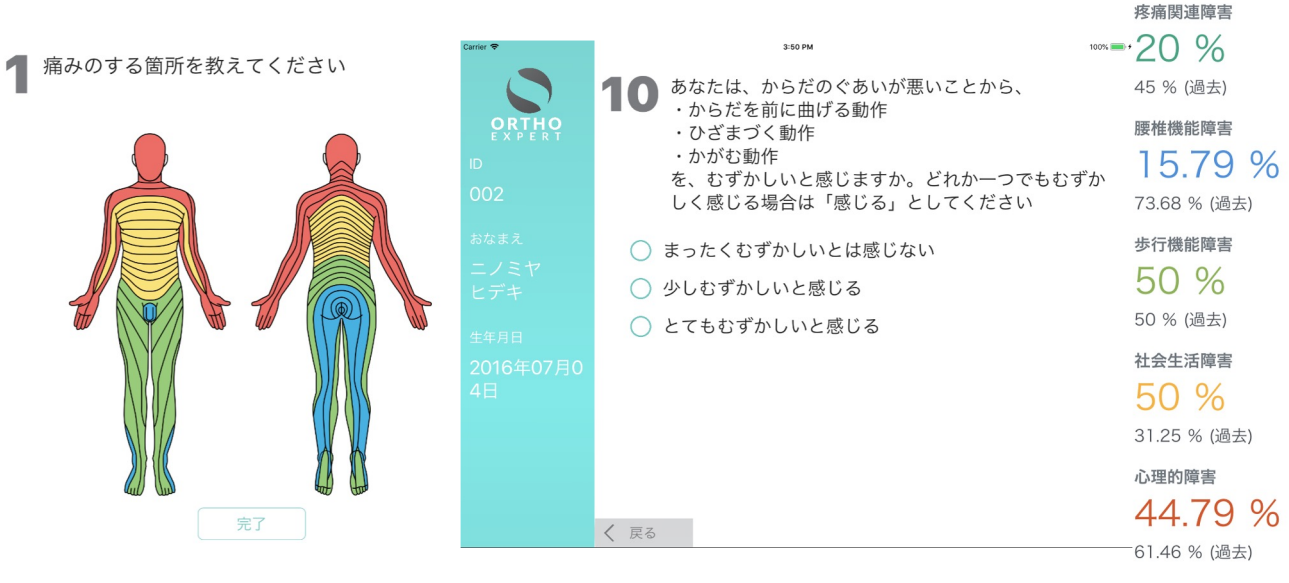
Hideki Ninomiya

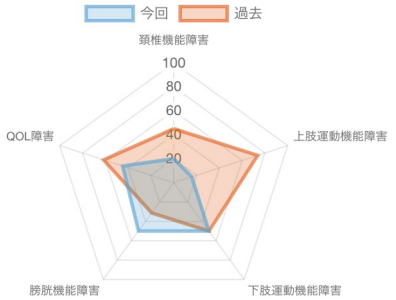


- Career
  - ○ LaSalle High School
  - ○ Tokyo University
  - ○ Neurosurgeon
  - ○ Medley
  - ○ 3idea
    - ■ Data Science
  - ○ Datack

The First Business： PRO system in spine surgery

- clinical support system & research support system
  - Oswestry Disability Index, Roland–Morris Disability Questionnaire
  - SF-12, EQ5D
  - Hospital Anxiety and Depression Scale



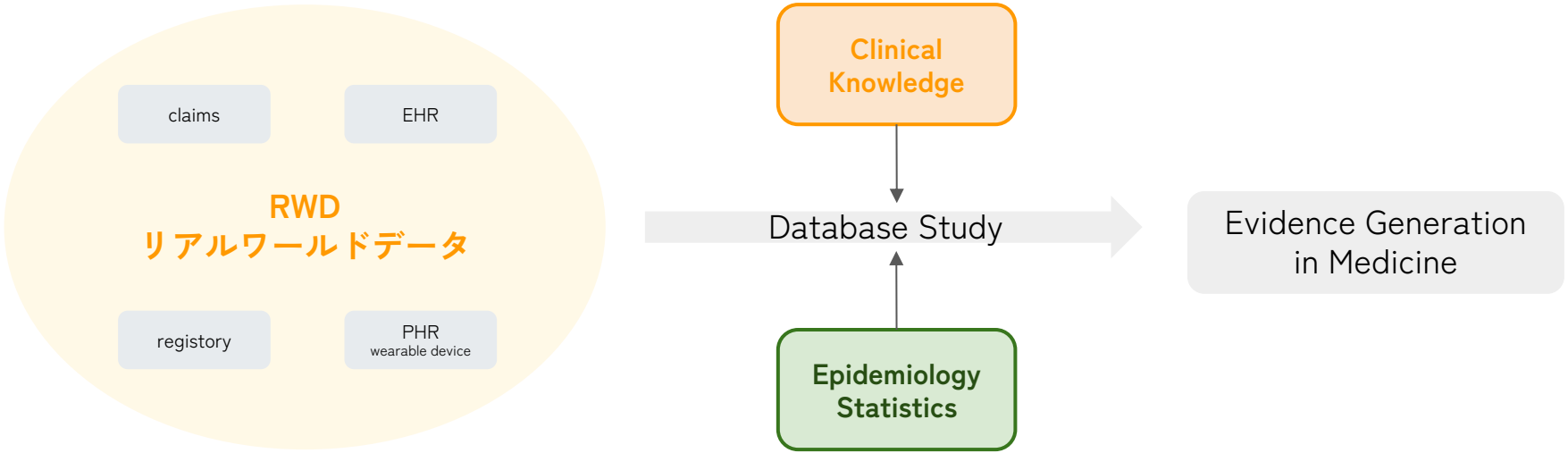


Natural Language Processing

- structuring from unstructured data using NLP

Now: Database Study Service

Through medical research, we contribute to the advancement of medicine and improve clinical practice.



※ データベース研究

4 Keys to driving innovation in RWD/RWE

4 Keys to driving innovation in RWD/RWE

1. Regulator/Consensus

1. Experience

1. Technology

1. Database

Breakthroughs in the last few years

1: Regulator/Consensus

Guidance to use RWE in their decision-making

United States of America Canada	October 2021	FDA draft Data Standards for Submissions Containing RWD
	November 2021	FDA draft Guidance Assessing Registries to Support Regulatory Decision-Making
	November 2021	US Congress Cures 2.0 Act draft Sec 304. Establishment RWE Task Force / Sec 309. Post-approval study requirements for accelerated approval using RWE
	December 2021	FDA draft Considerations for the Use of RWD/RWE To Support Regulatory Decision-Making
United Kingdom	December 2021	MHRA Guidance on the use of RWD Data in Clinical Studies to Support Regulatory Decisions
	December 2021	MHRA Guidance on RCTs using RWD to Support Regulatory Decisions
EU	October 2021	EMA Guideline on registry-based studies
	December 2021	EMRN Network Data Standardisation Strategy
	September 2022	DRAFT Good Practice Guide (RWD), Data Quality Framework
Australia	November 2021	TGA Real world evidence and patient reported outcomes in the regulatory context
Global	October 2021	ICH E8 (R1) General considerations for clinical trains now incl. use of RWD, external controls , and enriched studies

Regulatory Guidance in Japan

- 2021：「承認申請等におけるレジストリの活用に関する基本的考え方」について
- 2021：「レジストリデータを承認申請等に利用する場合の信頼性担保のための留意点」について
- 2022：レジストリ又は医療情報データベースのデータを医薬品の承認申請、再審査等申請に利用する場合の信頼性担保に係る留意点に関する質疑応答集（Q&A）について

RWD WG | 独立行政法人 医薬品医療機器総合機構

Marketing Authorization Applications Made to the European Medicines Agency

Characteristics of RWE included in new marketing authorization applications (MAAs) and extensions of indication (EOIs) for already authorized products submitted to the EMA in 2018 and 2019

	Initial MAA：63/158	EoI：28/153
approval	37/73	19/104
withdraw,rejection	4/26	1/8
under evaluation	20/59	8/41

Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What was the Contribution of Real-World Evidence?

Marketing Authorization Applications Made to the European Medicines Agency

Table 2 Use of RWD and RWE by ATC classification

ATC classification	Initial MAAs *n* with RWE / total assessed (%)	EOIs *n* with RWE / total assessed (%)
A Alimentary tract and metabolism	6/13 (46.2)	3/14 (21.4)
B Blood and blood forming organs	7/11 (63.6)	7/10 (70.0)
C Cardiovascular system	0/4 (0)	0/3 (0)
D Dermatologicals	0/1 (0)	0/3 (0)
G Genito urinary system and sex hormones	0/0 (0)	0/0 (0)
H Systemic hormonal preparations, excl. sex hormones, and insulins	1/8 (12.5)	0/0 (0)
J Anti-infectives for systemic use	14/25 (56.0)	1/19 (5.3)
L Antineoplastic and immunomodulating agents	23/61 (37.7)	12/78 (15.4)
M Musculo-skeletal system	1/1 (100)	2/2 (100)
N Nervous system	8/17 (47.1)	1/5 (20.0)
P Antiparasitic products, insecticides and repellents	0/0 (0)	0/0 (0)
R Respiratory system	1/8 (12.5)	1/14 (7.1)
S Sensory organs	2/6 (33.3)	0/2 (0)
V Various	0/3 (0)	1/3 (33.3)

ATC, Anatomical Therapeutic Chemical; EOIs, extension of indication; MAAs, marketing authorization application; RWD, real-world data; RWE, real-world evidence.

Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What was the Contribution of Real-World Evidence?

Marketing Authorization Applications Made to the European Medicines Agency

Whether RWE studies to support pre-authorization were included as main or supportive studies or a combination of both main and supportive		
Main study(ies)	3/20 (15.0)	4/16 (25.0)
Supportive study(ies)	15/20 (75.0)	12/16 (75.0)
Both main and supportive stud(ies)	2/20 (10.0)	0/16 (0.0)

Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What was the Contribution of Real-World Evidence?

Marketing Authorization Applications Made to the European Medicines Agency

Objective of RWE studies		
Safety	55/63 (87.3)	23/28 (82.1)
Efficacy	31/63 (49.2)	15/28 (53.6)
Disease epidemiology	5/63 (7.9)	3/28 (10.7)
Drug utilization	13/63 (20.6)	6/28 (21.4)
Abuse of drug	6/63 (9.5)	0/28 (0.0)
Other objectives	8/63 (12.6)	3/28 (10.7)

Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What was the Contribution of Real-World Evidence?

Marketing Authorization Applications Made to the European Medicines Agency

Data sources		
Electronic health care records from primary care	8/63 (12.7)	2/28 (7.1)
Electronic health care records from secondary care	8/63 (12.7)	0/28 (0.0)
Medical records from primary care[a]	8/63 (12.7)	5/28 (17.9)
Hospital data	20/63 (31.7)	7/28 (27.0)
Claims data	5/63 (7.9)	2/28 (7.1)

Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What was the Contribution of Real-World Evidence?

Marketing Authorization Applications Made to the European Medicines Agency

Characteristics of RWD/RWE studies used	Initial MAAs *n* (%) Total MAAs = 63	EOIs *n* (%) Total EOIs = 28
Prescription data	6/63 (9.5)	3/28 (10.7)
Dispensing data	5/63 (7.9)	1/28 (3.6)
All registries[b]	38/63 (60.3)	13/28 (46.4)
Disease registry	21/63 (33.3)	9/28 (32.1)
Product registry	9/63 (14.3)	3/28 (10.7)
Other registries[c]	13/63 (20.6)	2/28 (7.1)
Data from compassionate use program	2/63 (3.2)	1/28 (3.5)
Spontaneous reports[d]	4/63 (6.3)	3/28 (10.7)
Re-use of data from observational studies	4/63 (6.3)	1/28 (3.6)
Linked data sources	3/63 (4.7)	1/28 (3.6)
Other data sources[e]	18/63 (28.6)	5/28 (17.9)

Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What was the Contribution of Real-World Evidence?

Marketing Authorization Applications Made to the European Medicines Agency

Design of noninterventional studies, if used as RWE		
Cohort studies	56/63 (88.9)	22/28 (87.6)
Case-control	2/63 (3.1)	0/28 (0.0)
Cross-sectional	3/63 (4.7)	2/28 (7.1)
Other[f]	8/63 (12.6)	3/28 (10.7)

Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What was the Contribution of Real-World Evidence?

2: Experience

Recent Regulatory Desicions by RWE around the world

External Comparator	Amgen	Blinatumomab	B-cell precursor acute lymphoblastic leukemia in 1st/2nd complete remission w min.l residual diseease	2018 FDA 2019 EMA
	Amgen	Denosumab	Post menopausal women with osteoporosis at hige risk of fracture	2020 NMPA
	BMS	Abatacept	Prophylaxis of acute Graft vs Host disease in combo w CNI and MTX in hemotopoietic stem cell transplant	2021 FDA
	Genentech	Bevacizumab	Metastatic or recurrent squamous NSCLC in combination with platinum-based chemotherapy	2020 NMPA
	Merck/ Pfizer	Avelumab	Metastatic Merkel cell carcinoma	2017 FDA 2017 EMA
	Novartis	Onasemnogene abeparvovec-xioi	Pediatric(<2 yo) spinal muscular atrophy	2019 FDA
Pragmatic Randomized	Janssen	Paliperidone palmitate	Schizophrenia	2018 FDA
Historical Control	Astellas	Tacrolimus	Adult and pediatric lung transplant recipients	2021 FDA
	Chugai	Pertuzumab +trastuzumab	HER2+ colorectal cancer progression	2022 PMDA
Obserbational Study	Pfizer	Palbociclib	HR+,HER2- advanced/metastatic breast cancer in males	2019 FDA

Recent Regulatory Desicions by RWE in Japan

Approval year	Generic name	Indication	Data sourse
2011	Methotrexate	Rheumatoid arthritis	
2013	Tacrolimus	Interstitial pneumonitis in polymyositis / dermatomyositis	
2013	Methylprednisolone Sodium Succinate	Multiple sclerosis	
2013	Asfotase Alfa	Hypophosphatasia	
	大動脈用ステントグラフト	胸部大動脈瘤疾患	本臨床試験（治験群）は非盲検で実施し、ヒストリカルコントロールデータ（日本成人心臓血管外科手術データベースに収集された過去の外科手術成績）を対照群として有効性および安全性を検証した。

The endpoints were consistent across RWD sources and close to those in RCTs

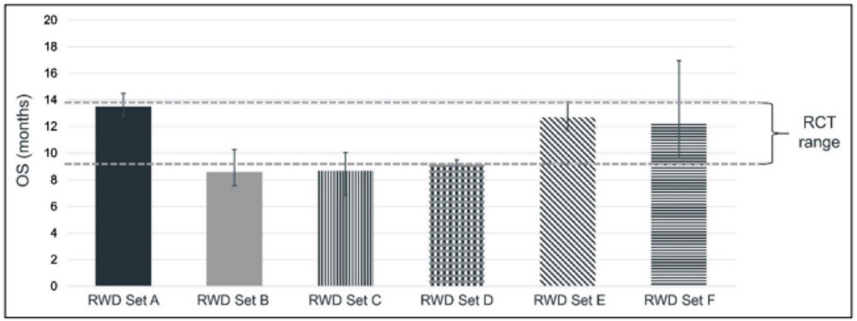


Figure 1. Comparing Overall Survival in RWD and RCT for Patients with Advanced Non-small Cell Lung Cancer Treated with Immune Checkpoint Inhibitors. Data sources include IQVIA, COTA, Flatiron, Kaiser Permanente Cancer Research Network, Mayo Clinic/Optum Labs, and The University of Iowa PCORnet.

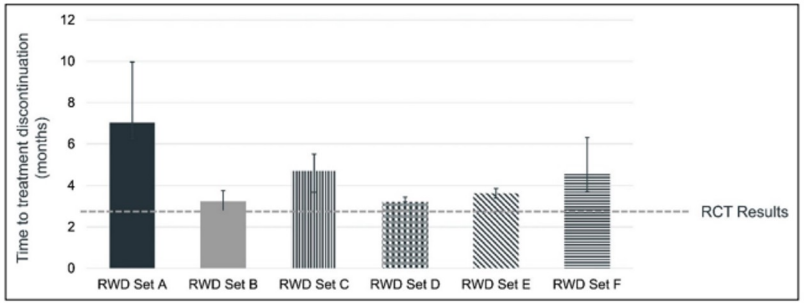


Figure 2. Comparing Time to Progression (Treatment Discontinuation) in RWD and RCT for Patients with Advanced Non-small Cell Lung Cancer Treated with Immune Checkpoint Inhibitors. Data sources include IQVIA, COTA, Flatiron, Kaiser Permanente Cancer Research Network, Mayo Clinic/Optum Labs, and The University of Iowa PCORnet.

- the same endpoints in patients with NSCLC. For OS, where RWD estimates were outside the 95% confidence limits observed in a meta-analysis of RCTs, they were short by only two weeks (a lower limit of 8.6 months vs. 9 months), which may reflect the true range of survival seen in RW settings
- Interestingly, time to progression measured by changes in treatment were always slightly longer in RW setting

Many Databases in the U.S.

- six “research-ready” RWD sources
  - IQVIA
  - COTA
  - Flatiron
  - Kaiser Permanente Cancer Research Network
  - Mayo Clinic/Optum Labs
  - The University of Iowa PCORnet

3: Technology

Limitations of human measurement

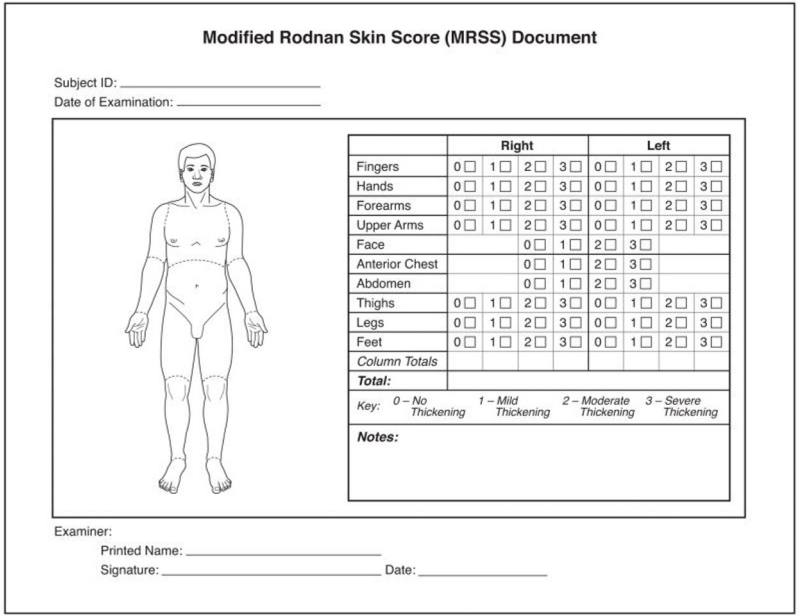
- Systemic Sclerosis
  - Endpoint: modified Rodnan total skin thickness score（mRSS）

東京大学 THE UNIVERSITY OF TOKYO

医師主導治験において、
全身性強皮症に対する B 細胞除去療法の長期(48 週間)にわたる有効性と安全性を確認

1．発表者：
吉崎　歩（東京大学医学部（皮膚科学）／東京大学医学部附属病院 皮膚科 講師）
江畑　慧（東京大学医学部附属病院 皮膚科 助教）
佐藤 伸一（東京大学大学院医学系研究科 皮膚科学／東京大学医学部附属病院 皮膚科 教授）

2．発表のポイント：
◆ 医師主導治験（注 1）として行われたプラセボ対照二重盲検並行群間比較試験（注 2）により、全身性強皮症に対するリツキシマブを用いた B 細胞（注 3）除去療法の 48 週間にわたる有効性と安全性が確認されました。
◆ 治験として行われた全身性強皮症に対するリツキシマブの臨床研究において、48 週間(およそ 1 年間)の長期データが得られたのは、世界で初めてのことになります。
◆ この医師主導治験における 24 週目までの結果によって、リツキシマブは全身性強皮症の新たな治療薬として 2021 年に保険承認されましたが、今回、より長期間の有効性と安全性が示されたことは、患者と医師が治療法を選択する際の一助となります。



Modified Rodnan Skin Score (MRSS) Document

Subject ID: _____
Date of Examination: _____

	Right				Left			
Fingers	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Hands	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Forearms	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Upper Arms	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Face			0☐	1☐	2☐	3☐		
Anterior Chest			0☐	1☐	2☐	3☐		
Abdomen			0☐	1☐	2☐	3☐		
Thighs	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Legs	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Feet	0☐	1☐	2☐	3☐	0☐	1☐	2☐	3☐
Column Totals								
Total:								

Key: *0 – No Thickening* *1 – Mild Thickening* *2 – Moderate Thickening* *3 – Severe Thickening*

Notes:

Examiner:
Printed Name: _____
Signature: _____ Date: _____

【プレスリリース】医師主導治験において、全身性強皮症に対するB細胞除去療法の長期（48週間）にわたる有効性と安全性を確認 | 東大病院
Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis.

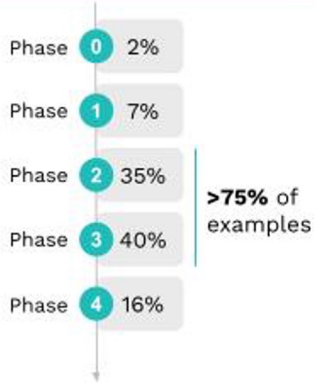
Digital Biomarker in Clinical Trials

DiMe's Crowdsourced Library of Digital Endpoints

Of the **101 Sponsors** that have collected digital endpoints...

Sponsors start digital endpoint development early

Digital Endpoints



**Only drug trials with reported phases are included*

Digital endpoints are being used across drug, device, biologic, and genetic product development

Investigational Product

Drug	51.4%
Device	33.9%
Biologic	8.7%
Other	5.7%
Genetic	.3%

Pharma trusts digital products, primary/ secondary endpoints

Endpoint Positioning

114	Primary endpoints
201	Secondary endpoints
20	Label Claim
6	Exploratory
25	Other

366 UNIQUE ENDPOINTS

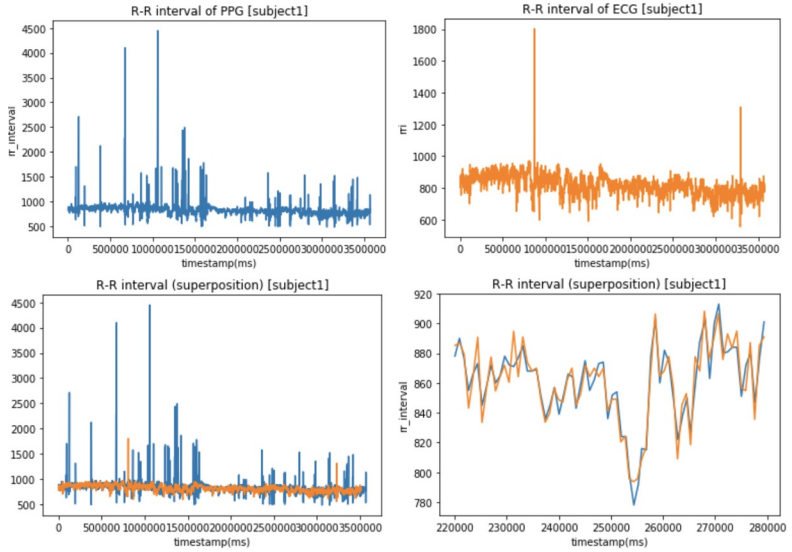
Is your company's work missing?
Submit it to DiMe:
https://bit.ly/DiMe-Endpoints

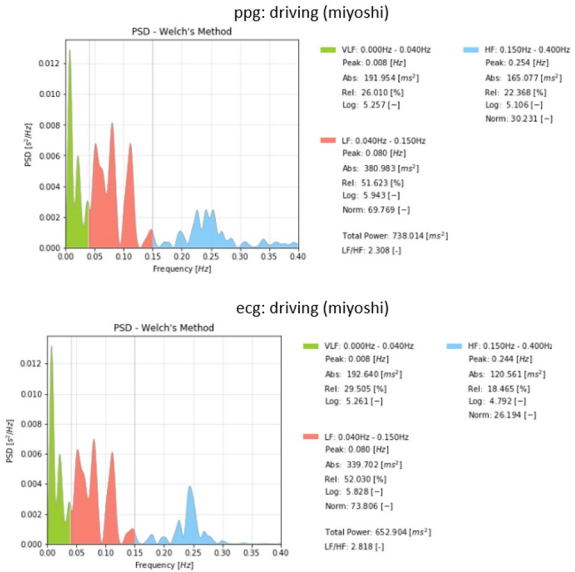
Source: https://www.dimesociety.org/index.php/knowledge-center/library-of-digital-endpoints

Last updated October 2, 2022

Predicting Drowsiness from Wearable Devices

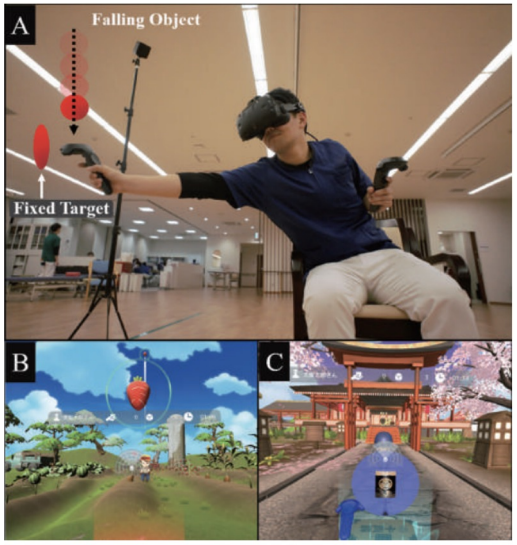
- Sleep stages were predicted from data (illuminance, acceleration, skin temperature, and optical pulse wave) acquired by a wristwatch wearable device.
  - EEG data as correct
  - Generate features such as heart rate, LF/HF, acceleration, etc.





mediVR KAGURA: virtual reality (VR)-guided rehabilitation

- Seated Virtual Reality-Guided Exercise based on Neuroscience／Behavioral science
- Three-dimensional tracking technologies.
- Improving walking ability(including balance) , ataxia, and attention disorder



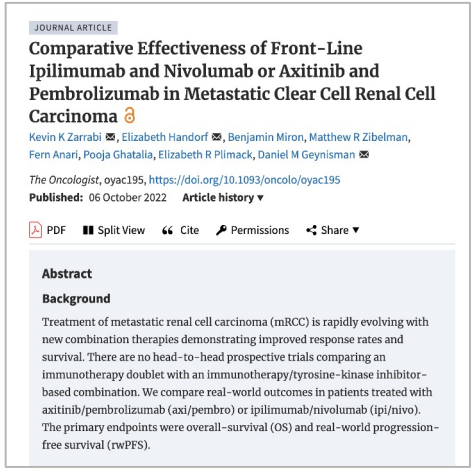
Virtual reality-guided dual-task body trunk balance training in a sitting position improved walking ability without improving leg strength.

Updates in Natural Language Processing Technology

- Task to extract information from research abstracts using RWD

- Question
  - what patient is targeted in the trial?
  - what was median OS for axi/pembro?
  - what was median OS for ipi/nivo?
  - what was rwPFS for axi/pembro?
  - what was rwPFS for ipi/nivo?

- MaRiOrOsSi/t5-base-finetuned-question-answering
  - Reference for Google's T5
  - fine-tuned for Generative Question answering
  - Not specialized in the medical field, but studied with general texts



JOURNAL ARTICLE

Comparative Effectiveness of Front-Line Ipilimumab and Nivolumab or Axitinib and Pembrolizumab in Metastatic Clear Cell Renal Cell Carcinoma

Kevin K Zarrabi, Elizabeth Handorf, Benjamin Miron, Matthew R Zibelman, Fern Anari, Pooja Ghatalia, Elizabeth R Plimack, Daniel M Geynisman

The Oncologist, oyac195, https://doi.org/10.1093/oncolo/oyac195

Published: 06 October 2022 **Article history**

PDF Split View Cite Permissions Share

Abstract

Background

Treatment of metastatic renal cell carcinoma (mRCC) is rapidly evolving with new combination therapies demonstrating improved response rates and survival. There are no head-to-head prospective trials comparing an immunotherapy doublet with an immunotherapy/tyrosine-kinase inhibitor-based combination. We compare real-world outcomes in patients treated with axitinib/pembrolizumab (axi/pembro) or ipilimumab/nivolumab (ipi/nivo). The primary endpoints were overall-survival (OS) and real-world progression-free survival (rwPFS).

Abstract

"Background

Treatment of metastatic renal cell carcinoma (mRCC) is rapidly evolving with new combination therapies demonstrating improved response rates and survival. There are no head-to-head prospective trials comparing an immunotherapy doublet with an immunotherapy/tyrosine-kinase inhibitor-based combination. We compare real-world outcomes in patients treated with axitinib/pembrolizumab (axi/pembro) or ipilimumab/nivolumab (ipi/nivo). The primary endpoints were overall-survival (OS) and real-world progression-free survival (rwPFS).

Patients and Methods

We used a de-identified database to select patients diagnosed with clear cell mRCC and treated with front-line axi/pembro or ipi/nivo from 2018 to 2022. Analyses are adjusted using propensity score-based inverse probability of treatment weighting, balancing age, gender, insurance, race, IMDC risk, and nephrectomy status. We compared survival by treatment groups using weighted and unweighted Kaplan–Meier curves with log-rank tests and weighted Cox proportional hazards regressions.

Results

We included a total of 1506 patients with mRCC who received frontline axi/pembro (n = 547) or ipi/nivo (n = 959). Median follow-up time was 20.0 months (range: 0.2-47.6). Baseline demographics were similar between the 2 cohorts. Adjusted median OS for the full population was 28.9 months for axi/pembro and was 24.3 months for ipi/nivo (P = .09). Twenty-four-month survival was 53.8% for axi/pembro treated patients and 50.2% for ipi/nivo treated patients. rwPFS was 10.6 months for axi/pembro treated patients and 6.9 months for ipi/nivo treated patients. Treatment with axi/pembro conferred improved survival in the IMDC favorable risk strata, with no significant difference in survival observed within the full cohort.

Conclusions

In this retrospective, real-world study of patients treated with front-line combination therapy, patients with IMDC favorable risk disease had better survival when treated with axi/pembro compared to ipi/nivo. However, survival for the entire population and the 24-month median overall survival were not statistically different between treatment groups. Longer follow-up is necessary to discern any emerging significant differences."

Successfully extracted median OS and rwPFS

```
[14] questions = [
        "what patient is targeted in the trial?",
        "what was median OS for axi/pembro?",
        "what was median OS for ipi/nivo?",
        "what was rwPFS for axi/pembro?",
        "what was rwPFS for ipi/nivo?"
    ]
```

- モデルに入力するテキスト (質問文 + ニュースレター該当箇所)

```
[16] sentences = [f"question: {question} context: {context}" for question in questions]
```

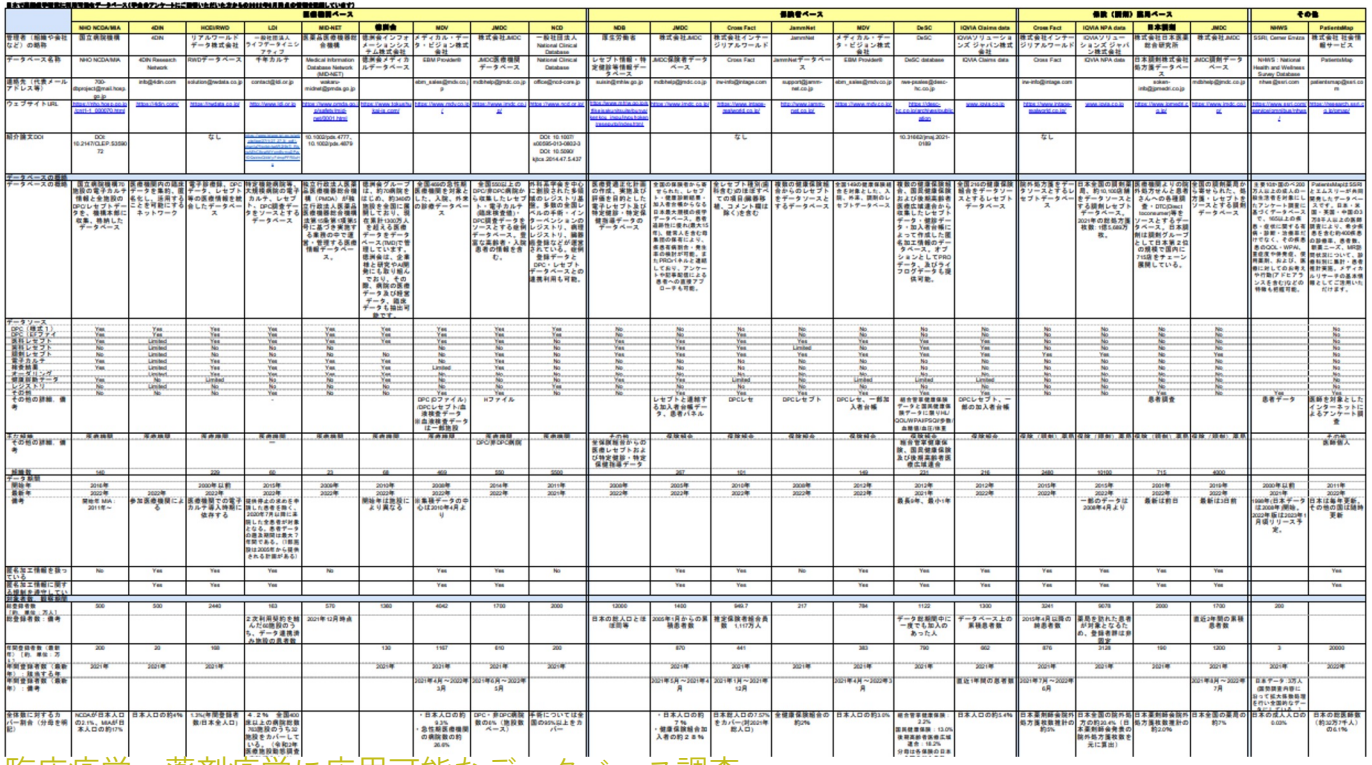
- 回答を生成させる

```
[20] model.to("cuda:0")

    for sentence in sentences:
        encoding = tokenizer.encode_plus(sentence, pad_to_max_length=True, return_tensors="pt")

        input_ids, attention_masks = encoding["input_ids"].to("cuda:0"), encoding["attention_mask"].to("cuda:0")

        outputs = model.generate(
            input_ids=input_ids, attention_mask=attention_masks,
            max_length=256,
            early_stopping=True
        )

        for output in outputs:
            line = tokenizer.decode(output, skip_special_tokens=True, clean_up_tokenization_spaces=True)
            print(line)

/usr/local/lib/python3.8/dist-packages/transformers/tokenization_utils_base.py:2336: FutureWarning: The `pad_to_max_length

clear cell mRCC patient
28.9 months
24.3 months
10.6 months
9.6 months
```

4: Database

More databases are available in Japan

- Japanese Society for Pharmacoepidemiology introduces 22 databases



日本における臨床疫学・薬剤疫学に応用可能なデータベース調査

Electronic Medical Record Databases

- Anonymized database
  - 4DIN
  - Yuimedi

- hospital information system
  - 徳洲会メディカルデータベース
  - 国立病院機構

- 次世代医療基盤法
  - 千年カルテ
  - DATuM IDEA / 凸版印刷

- Clinical Information Entry Support System
  - CyberOncology / PRIME-R

Summary

- We have been struggling with the limitations of RWD/RWE.

- The breakthroughs of the last few years to accelerate RWD/RWE.
  - Regulator/Consensus
  - Experience
  - Technology
  - Database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